



**Factors Influencing Clinical Trial Site Selection in Europe:  
The Survey of Attitudes towards Trial sites in Europe  
(The SAT-EU Study™)**

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**Factors Influencing Clinical Trial Site Selection in Europe:**  
**The Survey of Attitudes towards Trial sites in Europe**  
**(The SAT-EU Study™)**

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### Authors' contributions

MG: survey design and implementation; critical data analysis; manuscript drafting; overall project supervision

RT: survey design; statistical analysis; final manuscript editing

MM: survey design and implementation; survey advertising and data collection; critical data analysis; final manuscript editing

BC: survey design and implementation; survey advertising and data collection; critical data analysis; final manuscript editing

AP: survey design and implementation; survey advertising and data collection; critical data analysis; final manuscript editing

GG: survey design and implementation; critical data analysis; final manuscript editing

GA: survey design and implementation; critical data analysis; manuscript drafting; overall project supervision

### Data Sharing

Extra data is available in the form of raw survey data, providing individual (blinded) responses for each of 485 respondents. This data can be accessed either directly on the Survey Monkey platform or downloaded to excel from Survey Monkey. Our statistical analysis is also available upon request. Extra data is available by emailing [giuseppe.ambrosio@ospedale.perugia.it](mailto:giuseppe.ambrosio@ospedale.perugia.it)

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European Trial Site Selection Criteria - The SAT-EU Study™

Abstract (299 words)

**Objectives:** Applications to run clinical trials in Europe fell 25% between 2007 and 2011. Costs, speed of approvals, and shortcomings of European Clinical Trial Directive are commonly invoked to explain this unsatisfactory performance. However, no hard evidence is available on the actual weight of these factors. Furthermore, the possibility that other criteria may impact clinical trial site selection has never been investigated.

**Design:** The SAT-EU Study™ was an anonymous, cross-sectional Web-based survey that systematically assessed factors impacting European clinical trial site selection. It explored 19 factors across investigator-, hospital-, and environment-driven criteria, and costs. It also surveyed perceptions of the European trial environment.

**Setting:** Clinical Research Organizations (CROs), academic Clinical Trial Units (CTUs), and Industry invited to respond.

**Participants:** Responses obtained from 485 professionals in 34 countries: 49% from BioPharma, 40% from CTUs or CROs.

**Interventions:** None

**Outcome measures:** Primary: Weight assigned to each factor hypothesized to impact trial site selection and trial incidence; Secondary: Desirability of European countries to run clinical trials

**Results:** Investigator-, environment-, and hospital-dependent factors were rated highly important, costs being less important ( $P<0.0001$ ). Within environment-driven criteria, pool of eligible patients, speed of approvals, and presence of disease-management networks were significantly more important than costs or government financial incentives ( $P<0.0001$ ). The pattern of response was consistent across respondent groupings (CTU vs. CRO vs. Industry). Considerable variability was demonstrated in the perceived receptivity of countries to undertake clinical trials, with Germany, United Kingdom, and the Netherlands rated the best trial markets ( $P<0.0001$ ).

**Conclusions:** Investigator-dependent factors and ease of approval dominate trial site selection, while costs appear less important. Fostering competitiveness of European clinical research may not require additional government spending/incentives. Rather, carefully crafted harmonization of approvals, greater visibility of centres of excellence, and reduction of “hidden” indirect costs, may bring significantly more clinical trials to Europe.

Article summary (299 words)

### Article focus

- Applications to perform clinical trials in the EU fell 25% from 2007 to 2011, with bureaucracy, the EU clinical trial directive 2001/20/EC, and costs reportedly to blame. Yet, the clinical research community lacks a systematic assessment of the relative weight of these and other criteria that may impact the viability of conducting clinical trials in Europe.
- The SAT-EU Study compiled the input of 485 decision makers to: (a) systematically evaluate 19 factors possibly impacting site selection for multicentre trials for which Europe is under consideration, and (b) to assess the relative desirability of doing trials in 12 European countries. The web-based survey was blinded and response choices were scrambled

### Key Messages

- Costs, and even more so government incentives, carry a surprisingly low weight, while a number of investigator and environment-dependent factors dominate trial site selection decisions
- Not previously highlighted is the fact that the viability of conducting trials in Europe is also a function of the availability of critical information to get centres recruited and trials started, such as via participation in Disease Area Networks and web research portals
- Germany, UK, and the Netherlands are seen as the best trial markets

### Strengths and Limitations

- *Strength:* We provide systematic evidence across a large sample indicating that fostering competitiveness of European clinical research may not require additional government spending/incentives. We deliver convincing evidence to demonstrate that carefully crafted harmonization of approvals, greater visibility of centres of excellence via disease networks/the web, and reduction of “hidden” costs are more likely to boost competitiveness of European clinical research
- *Limitations:* Consistent with voluntary surveys, we could only analyse responses provided by those interested in replying, and therefore cannot exclude that other points of view may have emerged from those who did not participate; our questionnaire may also have missed potentially important factors

### Introduction

Europe has consistently expressed a desire to maintain and improve clinical trial competitiveness,<sup>1-3</sup> most recently by advocating a “European Research Area” in which “researchers, scientific knowledge and technology circulate freely.”<sup>4</sup> A major component of the European governance for clinical research, European Clinical Trial Directive 2001/20/EC (CTD) was intended to support this goal, focussing on the harmonisation of research processes across EU member states.<sup>5-9</sup> However, the CTD failed to achieve its intended impact on the simplification and harmonization of administrative provisions governing clinical trials<sup>9</sup>, and thus on the level of European clinical research activity.<sup>2,10-11</sup> In fact, from 2007 to 2011, the number of clinical trial applications in Europe fell 25%<sup>12</sup>. Accordingly, although concerted calls for further CTD revisions continue<sup>13-14</sup> and recommendations awaiting member state review have been made by European Commission<sup>6</sup> and endorsed by scientific societies,<sup>15</sup> it is not clear which specific recommendations should be implemented or prioritized at either national or pan-European level.

Much of this uncertainty stems from insufficient understanding of the key drivers determining decision made by the healthcare industry, academic clinical trial units (CTUs), and clinical research organizations (CROs) in selecting European trial sites. Furthermore, although it is widely believed that costs and speed of approval are key factors influencing clinical trial incidence in Europe,<sup>6,16</sup> the relative weight of these and other important criteria is poorly understood. To our knowledge, no published studies have examined country and site selection criteria for trials conducted in Europe. Evidence is therefore needed to improve our understanding of stakeholders’ decision-making process.

The Survey of Attitudes towards Trial sites in Europe (The SAT-EU Study™) was established as a non-profit collaborative effort to systematically assess factors impacting clinical trial site selection in Europe. We also investigated whether trial

selection needs differ between academic and commercial sponsors. Finally, the survey sought to explore perceptions of the current European trial environment, and to identify areas for future improvement.

## Methods

### *Survey design*

The SAT-EU Study was an anonymous web-based cross-sectional survey undertaken between September 26<sup>th</sup> 2011, and January 21<sup>st</sup>, 2012. It included all stakeholder groups involved in clinical trial site selection, i.e., BioPharma companies, medical device manufacturers, CROs, and CTUs. The survey sought to capture information on both early- and late-phase studies. Late-phase studies were defined as phase III for CTUs, BioPharma and their sub-contractors (i.e., CROs), and phase IV for other participants (e.g. medical device companies).

A multi-stage approach was used to develop the survey. First, we identified the main criteria expected to impact site selection. Second, we organized these in four broad categories: (i) investigator-related, (ii) hospital/Institution-related, (iii) country/environment-related, and (iv) costs (evaluated both separately and within the environment category). Third, the defined criteria underwent review and discussion with a small number of knowledgeable professionals to ensure that potentially relevant criteria had not been missed (Figure 1).

The study group then built an internet-based survey hosted on a freely-accessible online questionnaire software (Survey Monkey, Palo Alto, CA, USA). Before launching the survey, healthcare market research experts (The Planning Shop International, London, UK) reviewed the survey design to optimize content and minimize bias. Additionally, a pilot survey undertaken by 15 respondents in June 2011 was used to validate and refine question content and organisation.

*Survey Procedure*

The survey consisted of 23 questions, which took some 20 minutes to complete. In sequence, questions asked participants to (1) provide demographic information anonymously (2) rate the importance of each of the hypothesized trial site selection criteria for Europe as a whole, (3) provide perception of the trial environment in 12 European countries, and (4) rank areas of potential improvement. Participants' feedback was assessed using a multiple-choice format, requiring respondents to provide a single response of rank. The order of presentation of individual responses to each question was scrambled across respondents to minimise response bias. At the end of each section, a response box allowed respondents to provide open text comments. The full set of questions is accessible at [http://www.sbg-marcom.ch/sat-eu/Study\\_plan.html](http://www.sbg-marcom.ch/sat-eu/Study_plan.html)

The survey was advertised through Industry and Clinical Trial Associations, online communities, social networks, and personal contacts of the SAT-EU Study group<sup>17</sup>. No remuneration was provided to participants, but respondents were offered a summary of survey results.

*Statistical Analysis*

Given the descriptive nature of the SAT-EU study design, we did not formally estimate a required sample size. Instead, we sought to obtain at least 150 completed questionnaires from across the four stakeholder groups. Results are primarily presented descriptively as means (and 95% confidence intervals (95% CI)), or medians (and upper and lower quartiles), as appropriate to show results by group or country. Where data were available, responses were compared across three survey respondent groupings (i.e. CTU vs. CRO vs. industry), and across responses within each survey question, using one-way analysis of variance.

## Results

A total of 485 individual responses were obtained, with participants providing responses to 72% of questions on average. Responders represented over 100 different institutions, including over 50 pharmaceutical, biotechnology or medical device firms, and over 20 CROs and CTUs.

### *Respondent Demographics*

Respondents represented over 37 countries, the top five contributors being Italy, USA, UK, Germany, and Spain (Table 1). Participants were almost evenly split between BioPharma (49%) and CROs/CTUs (40%) (Figure 2). In terms of hierarchy/job description, 43% were vice-president, director, or manager in a research or marketing position, and an additional 20% were head of a CTU (Figure 3, Left Panel). The majority of respondents described themselves as being directly involved in trial site selection decisions; almost two-thirds either personally headed, or sat on the trial site selection committee of their organization (Figure 3 Right Panel). Importantly, most respondents were the final decision makers, stating that they were either the “overall final decision maker”, or that trial site selection decisions were “entirely at (their) discretion”.

**Table 1: Respondent work location (N=485)**

Country	Respondents
Australia	1
Austria	4
Belgium	21
Brazil	1
Bulgaria	3
Canada	6

China	1
Croatia	1
Czech Republic	1
Denmark	21
Egypt	1
Estonia	1
Finland	11
France	21
Germany	46
Greece	4
Hungary	4
India	13
Ireland	8
Israel	5
Italy	75
Netherlands	16
Nigeria	1
Norway	1
Poland	7
Portugal	9
Romania	7
Russia	1
Serbia	1
Slovakia	1
Slovenia	2
Spain	44
Sweden	13
Switzerland	20
Ukraine	1
United Kingdom	48
USA	58
Not Available	6

*Relevance of investigator, environment, hospital, and costs criteria*

Respondents were asked to divide 100 points (reflecting their perceived level of importance) across four categories of factors impacting trial site selection. For both early- and late-phase trials (as defined in Methods), factors pertaining to the investigator, the hospital/unit, and the environment, were rated at a high level of importance (25 or above) (Figure 4). When combined, investigator- and hospital-

dependent levers were reported to be instrumental in trial site choice for both early- and late-phase studies (average weight 60/100 and 57/100 respectively). In contrast, cost factors were considered to be less important for both early- and late-trials ( $P<0.0001$ ) (Figure 4). This pattern of response was consistent across survey respondent groupings (i.e. CTU vs. CRO vs. industry; not shown).

### *Environment-Driven Criteria*

To explore environmental dynamics, respondents were asked to assign 100 points across six environment-related criteria. Market size/pool of eligible patients in the region, speed of approvals, and presence of disease management networks, were assigned a greater level of importance. In contrast, costs of running trials, and particularly government financial/tax incentives were considered to be of significantly lower importance ( $P<0.0001$ ) (Figure 5). Also in this case, the pattern of response was consistent across survey respondent groupings (not shown).

### *Investigator-Driven Criteria*

Respondents were asked to assign 100 points across five investigator-related criteria. There was a statistically significant difference in the level of importance of the factors tested, with investigator track record in prior trials, experience in similar studies, and interest in study scoring a level of importance of 20 or above, while concurrent trial workload, and publication track record were significantly less important ( $P<0.0001$ ) (Figure 6). The pattern of response was again consistent across survey respondent groupings (not shown).

### *Hospital-Driven Criteria*

In this domain, 100 points had to be assigned across six criteria that explored characteristics of the specific hospital/unit where a clinical trial may potentially be run.

There was a statistically significant difference in the level of importance of hospital-driven criteria, whereby site personnel experience and training, respondent's previous experience with site, and availability of facilities and equipment required by trial scored above 20 ( $P<0.0001$ ). In contrast, site personnel language capabilities and hospital quality assurance process were significantly less important (Figure 7).

*Perception of European Trial Environment*

Our survey showed a statistically significant difference in respondents' perceived desirability of running clinical trials across the twelve EU countries tested, i.e., Europe's top 5 healthcare markets (Germany, France, Italy, the UK, and Spain), large east European markets (Poland, Hungary, Czech Republic), plus Netherlands, Belgium, Switzerland, and Austria. For both accessibility and transparency of all information required to run clinical trials (Figure 8 Upper Panel), and availability of equipment (not shown), Germany, UK and the Netherlands were the top three scorers. With regard to predictability and speed of Ethics Committees, Belgium was the top scorer, followed by Germany and the Netherlands (Figure 8 Lower Panel). In terms of overall trial site "desirability", respondents scored Germany as the most desirable trial location, followed by the Netherlands and UK ( $P=0.0001$ ) (Figure 9).

*Possible Improvements*

Two questions tested the hypothesis that making a site more visible would be desirable from the decision-makers' perspective. We found that 83% of respondents would have been "much more likely" to include a site if all relevant investigator- and hospital-related information were readily available (Figure 10 Left Panel). Furthermore, 75% believed that web-site information would be either "definitely welcome", or "useful most of the time" (Figure 10 Right Panel).

## Discussion

The SAT-EU Study<sup>TM</sup> was a web-based survey designed to identify perceived drivers and hurdles associated with conducting clinical trials in Europe. We obtained responses from over four hundred participants in key stakeholder groups, i.e. BioPharma industry, medical device manufacturers, CROs, and CTUs. The vast majority of countries actively involved in clinical trials were represented, while most respondents were key decision makers in their organizations. These features allowed us to get direct and potentially relevant insights into the reasoning behind site selection for clinical trials.

Recent years have seen much public policy discussion on the need to foster Europe's role in medical research, and to rekindle its dwindling attractiveness for investment in clinical trials.<sup>18-20</sup> Various strategies have been proposed based on a "common sense" approach. Whilst possibly sound, policy recommendations were typically not founded on a systematic understanding of factors impacting clinical trial site selection. Indeed, one could argue that, borrowing from the rigour of its own discipline, medical policy decisions at all levels ought to be "evidence-based". Regretfully however, this approach seems to be largely absent. To our knowledge, the SAT-EU study is the first effort aimed at systematically investigating factors impacting trial site attractiveness across Europe. Given the survey's size, the variety of domains explored, the number of countries and organizations involved, and the prevalence of senior decision makers, our results may provide insight into "real world" trial site decisions.

Our study has several key findings. First, there was evidence of considerable variability in the perceived receptivity of European countries to undertake clinical trials, Germany, United Kingdom, and the Netherlands being rated the best markets. Reasons for greater appeal of certain countries are multiple. Larger countries could be

more attractive because of greater patient recruitment potential, and in prospect, because of the size of their markets. However, country size does not entirely explain the phenomenon, given the excellent results of small countries such as the Netherlands, and the low score of large countries such as Italy or Spain. Our survey sheds some light on this by pointing to the negative impact of administrative burden on clinical trial competitiveness. This is not only a concern at country level. Central to this discussion is the notion that the time required to collect information to determine a site's feasibility for inclusion in a trial, and to get it started, is also critical. Hence, the high weight placed on a site's proven track record in efficiently delivering results, which bears a relationship to specialized clinical research centres, and equally important, to the ability of clinical trial sponsors and organizers to access all of the required information quickly and effectively. Accordingly, the downsides of operating within a sub-optimal regulatory environment may not prejudice selection of an otherwise visible and competent investigator, whose trial site information is readily available and who is able to recruit the required patients. A third important finding of our survey is that contrary to a widely held tenet, costs of running trials - often invoked to explain why industry is going outside Europe<sup>6,16</sup> - as well as government incentives/tax breaks, are not the main considerations when selecting European sites. Although apparently surprising, the limited impact of costs needs to be considered against the backdrop of the various issues to which our survey tried to provide a response. Indeed, in addition to "direct" costs, a major negative factor is represented by indirect, or "hidden" costs, such as those characterized by time lost through layers of bureaucracy, slow recruitment by sites, or poor overall site performance. Hence, the importance of not only bureaucracy, but also of the level of training and trial expertise at sites. Additionally, the notion that investments in clinical trials in Europe cannot be easily improved through government incentives or tax breaks may have important implications in terms of public policy. Our survey clearly indicates that stakeholders

would like a single European “trial market” allowing them to gear trial site selection to expert investigators and to optimal patient recruitment, unobstructed by heterogeneous regulations or hurdles to obtaining crucial information. Participants expressed this need in two main ways. First, from a regulatory or “macro” perspective, they expressed desire for easier approval processes with less national variability and stronger pan-European element. This may indicate ethical committee approval timeframes, as well as institutional approvals at site level. Second, from a clinical research or “micro” perspective, respondents want access to transnational networks of disease-area experts, through visibility of experienced trial units via the internet and/or via participation in disease networks.

More than 50 years ago, the founders of the European Union envisioned a single market at the core of the European project. Despite this, a “single market” vision for clinical research did not develop as envisaged. This is damaging to an industry in which much of the investment in clinical trials is by necessity multinational. Indeed, Europe’s 2020 growth strategy calls for 3% of its Gross National Product to be invested in research and development (R&D) by 2020<sup>21</sup>. If this goal is to be achieved, BioPharma - the European sector with the highest R&D/Sales ratio<sup>22</sup> - should be allowed to invest in Europe without facing unnecessary roadblocks. Given the size of its healthcare market, its aging population, its well-established pharmaceutical industry, and the quality of its research centres and investigators, Europe has a formidable comparative advantage in clinical research. Individual European member states are well poised to take advantage of this by making the EU more competitive in clinical research. They should be encouraged to do so, not simply by investing in incentives or tax breaks, but by implementing revisions to the CTD that are under consideration by member states, and by legislating removal of unhelpful bureaucratic barriers at national level. Improving hospital contracting, such as via national or even pan-European contract templates, would also significantly reduce administrative burden, speed up

trial start, and make the European landscape significantly more competitive. On their part, the research community and relevant national bodies have a parallel imperative to ensure that hospitals and institutions are organised and networked more effectively, and that there is adequate training of trial staff. They need to ensure that clinical centres wishing to undertake more research are made more visible to industry and to international research communities, through dedicated research portals on their web sites, or by creating and/or joining disease networks. Finally, given that selected countries are consistently scored above others, a best practice audit of administrative provisions governing and supporting clinical trials in countries such as Germany, the UK, the Netherlands<sup>14</sup> would be helpful for drawing policy implications for other countries. The case for action rests on the realization that evidence-based policy is indeed possible in this arena. Learning from what is working successfully will facilitate the road to creating a more welcoming environment for clinical research in Europe.

**Limitations**

Consistent with voluntary surveys, we could only analyse responses provided by those who were interested in replying, and therefore we cannot exclude that other points of view may have emerged from those who did not participate. However, the number and range of people who have taken the time to respond to this survey is encouraging, as is the finding that most of them were the final decision makers in the process, and that they belonged to a variety of organizations from a number of countries. Whilst we took care in designing a survey that focused on the key determinants of trial site selection, we may have missed potentially important issues. We tried to minimize this through preliminary survey review and refinement with the help of external experts. Finally, some of our questions in relation to process and speed of approval may need further research to determine the root issues, as problems differ from country to country, and have to be weighed against the need to ensure that

patient safety remains unprejudiced.

## Conclusions

Our study shows that fostering European clinical research and attracting more trials to Europe does not require additional government spending. Instead, it requires harmonised national adoption of revisions to the CTD, greater visibility of transnational networks of disease experts, and greater accessibility to research system at national and pan-European levels. Carefully crafted harmonization of approvals, including aligned hospital contracting and greater visibility of centres of excellence may bring significantly more clinical research to Europe. Europe needs growth, and clinical research can play its part in directly stimulating economic activity while simultaneously boosting European innovation.

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Applied Clinical Trials (ACT)

<http://www.appliedclinicaltrialsonline.com/>

European Forum for Good Clinical Practice (EFGCP)

<http://www.efgcp.be>

European Federation of Pharmaceutical Industry Associations (EFPIA)

<http://www.efpia.eu/>

European Biotech Industry Association (EuropaBio)

<http://www.europabio.org/>

Perugia University, Italy

<http://facolta.unipg.it/medicina/>

Drug Information Association (DIA)

<http://www.diahome.org/DIAHome/Home.aspx>

Virtuoso Consulting, Geneva, Switzerland

<http://www.virtuoso.ch/model.html>

European Vision Institute Clinical Research Network (Disease Network)

<http://www.evicr.net>

EUCOMED Clinical Trial Interest Group

<http://www.eucomed.be/>

Pharma IQ

<http://www.pharma-iq.com/>

## Competing Interests

All co-authors work in the area of healthcare, either academia or consulting, and as such have all been, or are involved in, the initiation, execution or interpretation of clinical trials. Accordingly, all co-authors have an intellectual/academic interest in seeing the European Clinical trial industry enhance its competitiveness. None of the authors however, stands to gain any more than any other member of the European healthcare community from the implementation of any of the recommendations made in the manuscript. We declare no other conflict of interest, and no other relationships or activities that could appear to have influenced the submitted work.

The study group has received acknowledgement permission from each of the institutions acknowledged for having helped to collect survey participants. Participation in the survey was voluntary and not associated with any remuneration.

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## Figure Legend

### Figure 1

Four categories of levers potentially impacting trial site selection were identified. Survey weighed relevance across these four levers, then drilled down for weight within each sub-category.

### Figure 2

Distribution of Organisation to which respondents belonged (self reported)

Respondents were asked to answer the question: "Please indicate which organisation most closely resembles yours"

Bars show percent distribution of 485 individual responses

#### Abbreviations

- Pharma = Industry: Pharmaceutical Company
  - CRO = Clinical Research Organisation
  - CTU = Academic Clinical Trial Unit
  - Biotech = Industry: Biotechnology Company
- Medical Devices included: Medical Devices, Radiological, Electro-medical or HealthCare Information Technology

"Other" included following self-reported categories:

- Respondent working for a mixed portfolio industry with either Pharma/Biotech portfolio or Pharm/Medical Device portfolio (self reported)
- Regulatory/Clinical Consultant
- Hospital or private clinic

### Figure 3

#### Left Panel: Respondent hierarchy

Respondents were asked to answer the question: "Please indicate the position which most closely resembles yours"

Chart shows percent distribution of 485 individual responses

VP = Vice President

CTU = Clinical Trial Unit

CRO = Clinical Research Organisation

"Others" were respondents who wanted to be more specific in their titles:

- Global Study Manager/Clinical Research Associate
- Regulatory Affairs/ Regulatory in a Clinical department/ Good Clinical Practice Quality Assurance Manager, or Director/ Safety Pharmacovigilance Officer
- Medical Affairs/ Medical Director/Clinical Director/Global Scientific Affairs
- General Manager
- "Professor or Lecturer"

#### Right Panel: Respondent organisation's decision-making process

Respondents were asked to answer the question: "Please indicate which most closely resembles how trial site selection decisions are made at your institution"

Chart shows percent distribution of 485 individual responses

- Other included:
- My staff decides
  - Decision outsourced to CRO
  - CRA decides
  - Decisions according to Standard Operation Procedures
  - Many people involved in decision, or Study Team decides
  - Our affiliates decide

**Figure 4: Levers impacting trial site selection for early and late trials**

Respondents were asked to divide 100 points across the below 4 levers impacting their trial site selection for early phase studies:  
(Pharma, Biotech, CROs, CTUs, answer for phase II studies)  
(Medical device and all others answer for phase III studies)

and then for later phase studies:  
(Pharma, Biotech, CROs, CTUs, answer for phase III studies)  
(Medical device and all others answer for phase IV studies)  
Bars represent mean and 95% Confidence Interval (N=341)

There was evidence of a statistically significant difference in the level of importance among the 4 factors ( $P < 0.0001$ )

**Figure 5: Environment-driven criteria in selection of trial sites of phase II–III study sites (phase III–IV for medical devices)**

Respondents were asked to rate environment-driven criteria by dividing 100 points across 6 criteria potentially relevant in selecting trial sites for phase III studies:  
(Pharma, Biotech, CROs, CTUs, answer for phase III studies)  
(Medical device and all others answer for phase IV)  
Bars represent mean and 95% Confidence Interval (N=341)

There was evidence of a statistically significant difference in the level of importance among the 6 criteria ( $P < 0.0001$ )

**Figure 6: Investigator-driven criteria in selection of trial sites of phase II–III study sites (phase III–IV for medical devices)**

Respondents were asked to rate investigator-driven criteria by dividing 100 points across 5 criteria potentially relevant in selecting trial sites for phase III studies:  
(Pharma, Biotech, CROs, CTUs, answer for phase III studies)  
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Bars represent mean and 95% Confidence Interval (N=341)

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**Figure 7: Hospital-driven criteria in selection of phase II–III study sites (phase III–IV for medical devices)**

Respondents were asked to rate Hospital driven criteria by dividing 100 points across 6 criteria potentially relevant in selecting trial sites for phase III studies:  
(Pharma, Biotech, CROs, CTUs, answer for phase III studies)  
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Bars represent mean and 95% Confidence Interval (N=342)

There was evidence of a statistically significant difference in the level of importance among the 6 criteria ( $P < 0.0001$ )

#### Figure 8

##### Upper Panel

##### **Accessibility and transparency of all types of information required to make trial site selection decisions - Twelve country rank**

Respondents were asked to rate twelve countries for the accessibility and transparency of information (of all types) required to make trial site selection  
Bars represent mean and 95% Confidence Interval (N=296)

Statistically significant difference in satisfaction across EU countries ( $P = 0.0001$ )

##### Lower Panel

##### **Predictability and speed of Ethics Committees and IRBs for phase II–III multi-centre RCTs - Twelve country rank**

Respondents were asked to rate twelve countries for the speed of their ethics committees & IRBs for phase III (3) multi centric RCTs  
Bars represent mean and 95% Confidence Interval (number of respondents in parentheses)

Statistically significant difference in satisfaction across EU countries ( $P = 0.0001$ )  
IRB = institutional review board

#### Figure 9: Trial Site Desirability by country

Trial Site Desirability "Index" - Nine Country Rank

Respondents were asked to provide their "personal perception" ranking of the desirability of running trials in 9 countries, ranking them from (1) "most desirable" country to (9) "least desirable" country (if needed, they could click "no opinion" in up to three countries they know the least)  
Data are presented as whisker-box plot of median and lower and upper quartile

There was evidence of a statistically significant difference in the perceived desirability of running trials across EU countries ( $P = 0.0001$ )

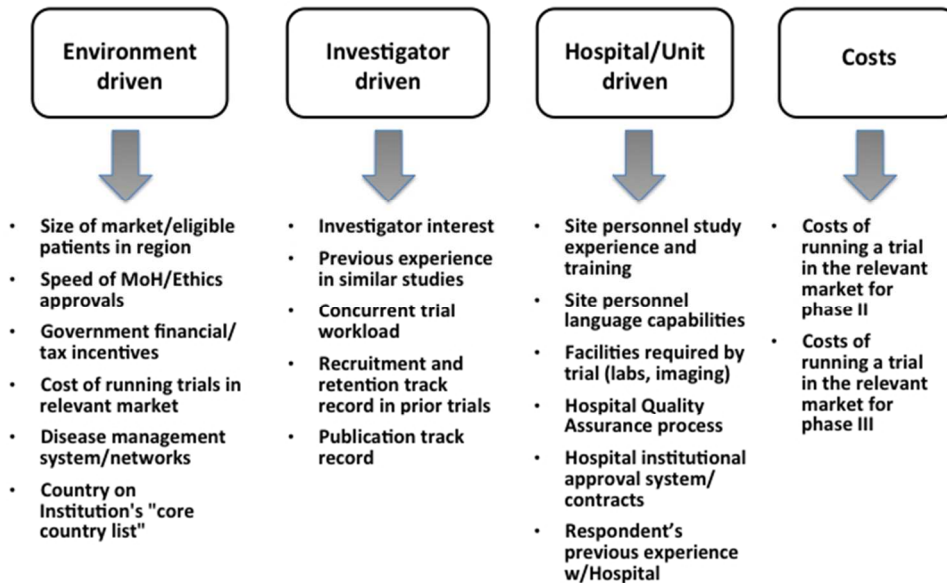
**Figure 10**  
**Left Panel: Likelihood of selecting trial site given relevant information**

Respondents were asked to rate their level of agreement with the statement:  
“I am much more likely to select a trial site if I have all of the relevant Investigator and Site specific information easily available to me”  
Chart represents percent response (N=253)

**Right Panel: Usefulness of trial site web site information**

Respondents were asked to pick the statement that they felt closest to with reference to the assertion that “it would be useful to have relevant trial information readily visible in a dedicated public section the Hospital's web site (Facilities, equipment, personnel qualification, Ethics Committee and Institutional Review Board timings, contact people for trials, etc.)

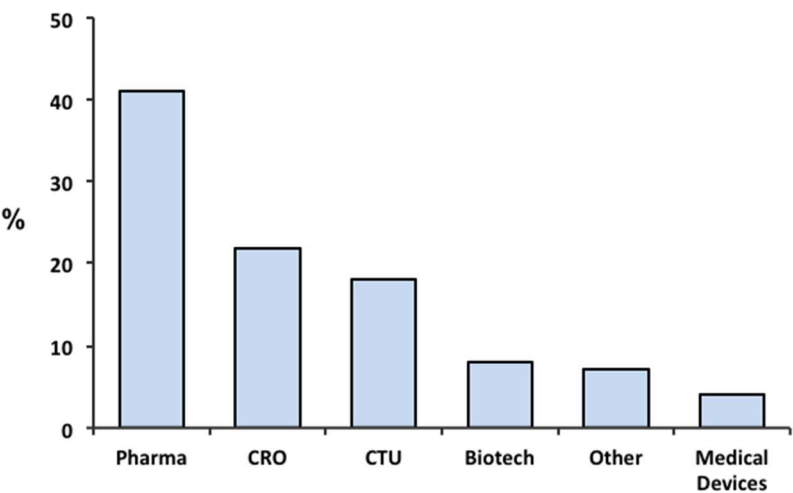
*Figure 1*  
**Hypothesis about trial site selection criteria**



Four categories of levers potentially impacting trial site selection were identified. Survey weighed relevance across these four levers, then drilled down for weight within each sub-category.

254x190mm (72 x 72 DPI)

Figure 2  
Respondents' Organisation



Distribution of Organisation to which respondents belonged (self reported)

Respondents were asked to answer the question: "Please indicate which organisation most closely resembles yours"

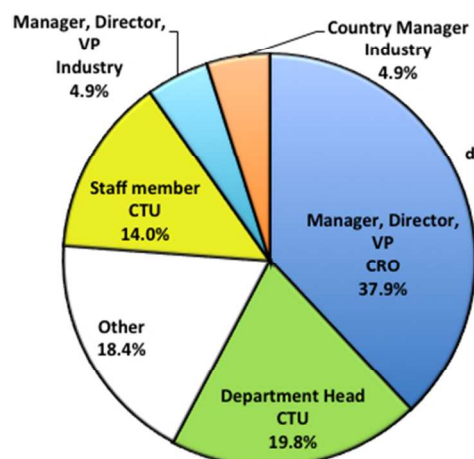
Bars show percent distribution of 485 individual responses

Abbreviations

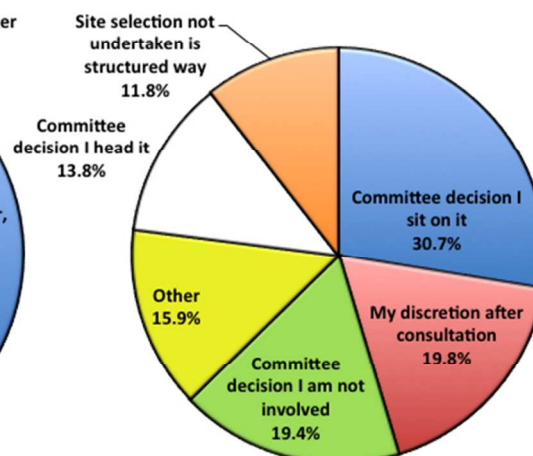
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*Figure 3 Left Panel*  
**Respondents' Hierarchy**



*Figure 3 Right Panel*  
**Respondent organisation's decision-making process**



Respondents were asked to answer the question: "Please indicate the position which most closely resembles yours"

Left Panel: Respondent hierarchy

Chart shows percent distribution of 485 individual responses

VP = Vice President

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"Others" were respondents who wanted to be more specific in their titles:

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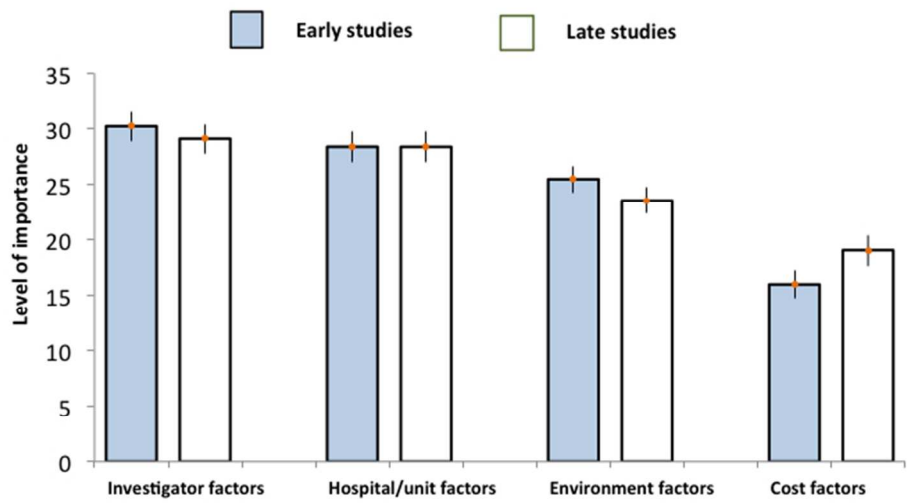
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Figure 4  
Levers impacting trial site selection for early and late trials



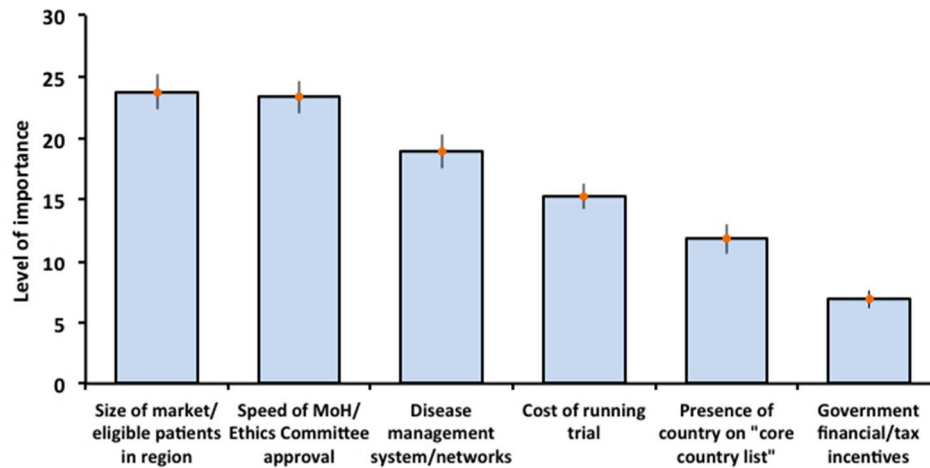
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and then for later phase studies:  
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Bars represent mean and 95% Confidence Interval (N=341)

There was evidence of a statistically significant difference in the level of importance among the 4 factors (P < 0.0001)

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*Figure 5*  
**Environment-driven criteria in selection of trial sites**



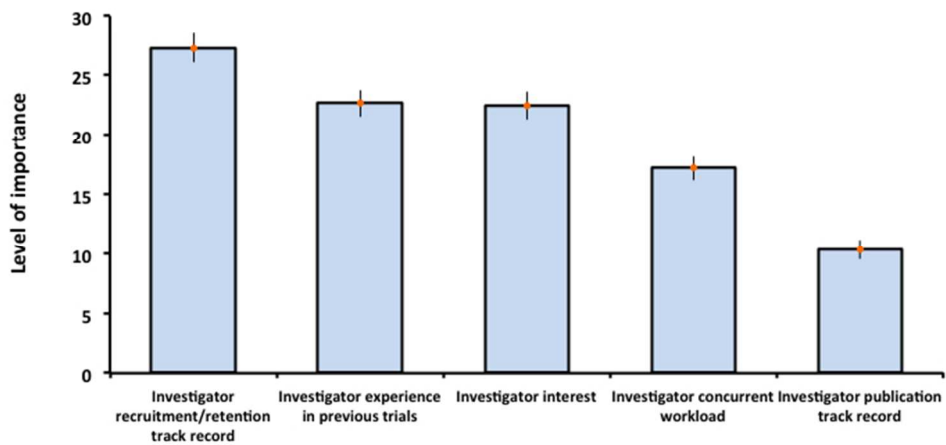
Respondents were asked to rate environment-driven criteria by dividing 100 points across 6 criteria potentially relevant in selecting trial sites for phase III studies:  
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There was evidence of a statistically significant difference in the level of importance among the 6 criteria ( $P < 0.0001$ )

254x190mm (72 x 72 DPI)

Figure 6

Investigator-driven criteria in selection of trial sites

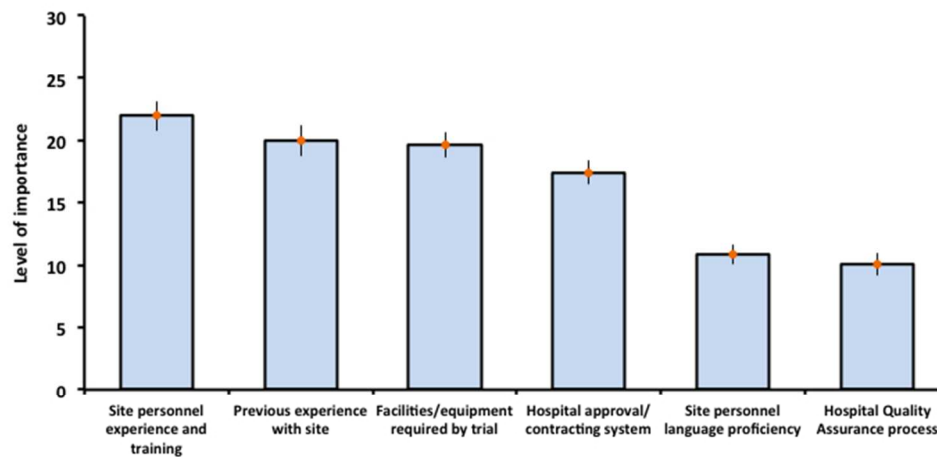


Respondents were asked to rate investigator-driven criteria by dividing 100 points across 5 criteria potentially relevant in selecting trial sites for phase III studies:  
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*Figure 7*  
**Hospital-driven criteria in selection of trial sites**



Respondents were asked to rate Hospital driven criteria by dividing 100 points across 6 criteria potentially relevant in selecting trial sites for phase III studies:  
 (Pharma, Biotech, CROs, CTUs, answer for phase III studies)  
 (Medical device and all others answer for phase IV)  
 Bars represent mean and 95% Confidence Interval (N=342)

There was evidence of a statistically significant difference in the level of importance among the 6 criteria ( $P < 0.0001$ )

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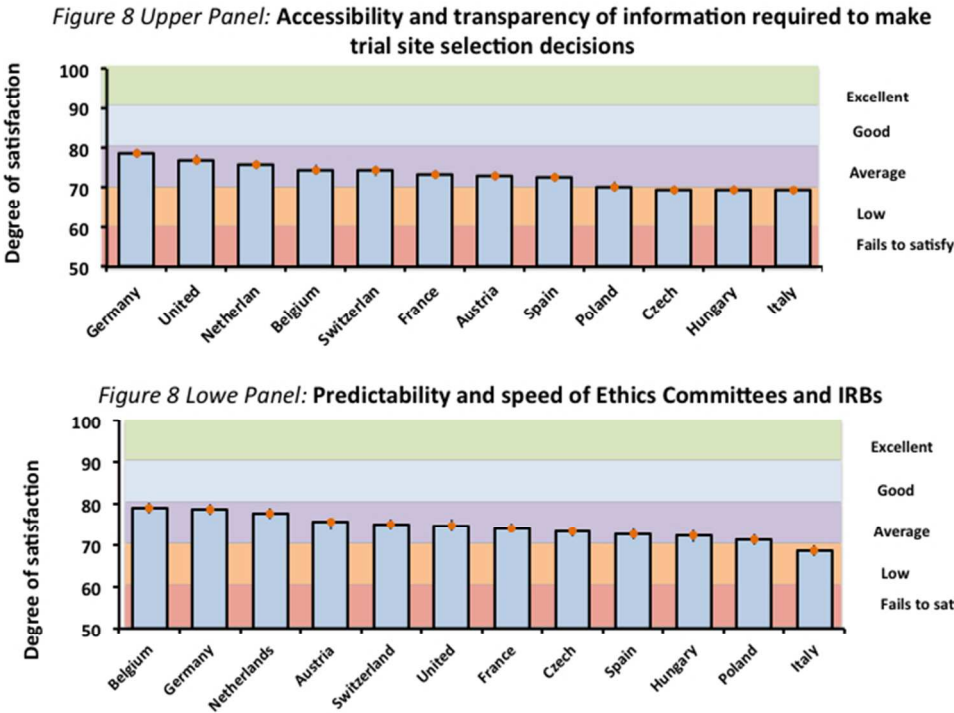
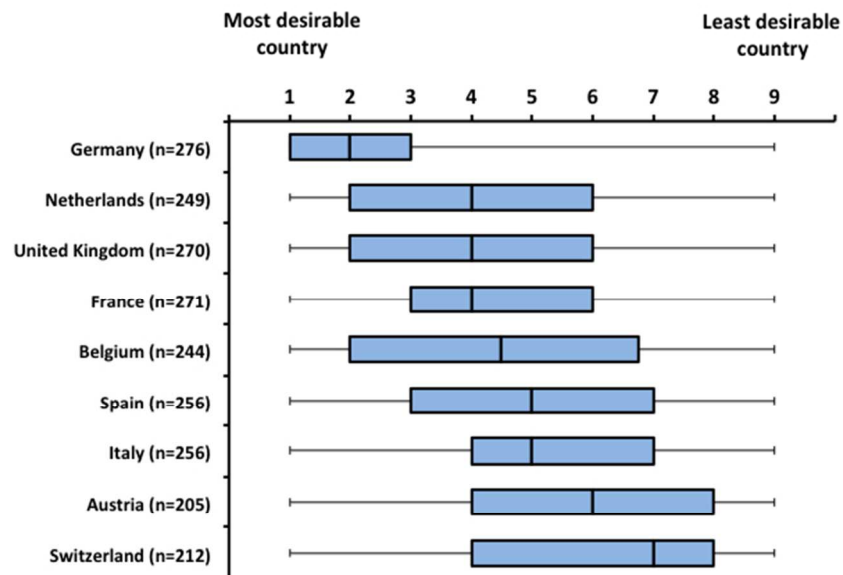


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Accessibility and transparency of all types of information required to make trial site selection decisions - Twelve country rank  
Respondents were asked to rate twelve countries for the accessibility and transparency of information (of all types) required to make trial site selection  
Bars represent mean and 95% Confidence Interval (N=296)  
Statistically significant difference in satisfaction across EU countries (P = 0.0001)

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Predictability and speed of Ethics Committees and IRBs for phase II-III multi-centre RCTs - Twelve country rank  
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Respondents were asked to provide their "personal perception" ranking of the desirability of running trials in 9 countries, ranking them from (1) "most desirable" country to (9) "least desirable" country (if needed, they could click "no opinion" in up to three countries they know the least)

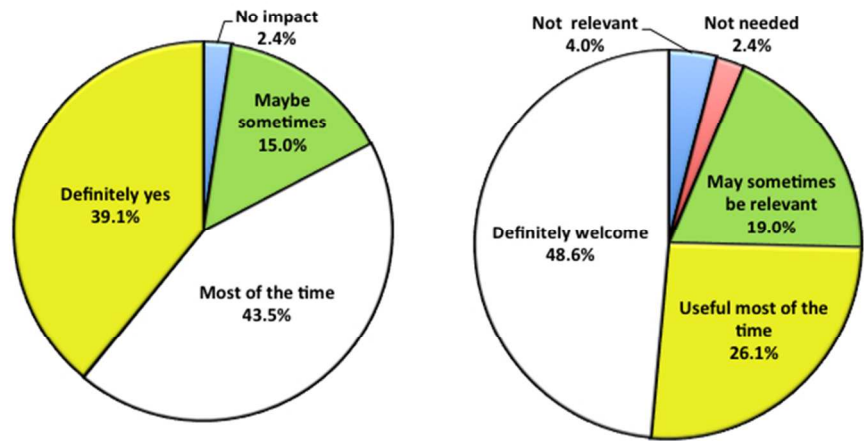
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There was evidence of a statistically significant difference in the perceived desirability of running trials across EU countries ( $P = 0.0001$ )

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*Figure 10 Left Panel*  
**Likelihood of selecting trial site given relevant information**

*Figure 10 Right Panel*  
**Usefulness of trial site web site information**



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Respondents were asked to rate their level of agreement with the statement:  
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Chart represents percent response (N=253)

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Respondents were asked to pick the statement that they felt closest to with reference to the assertion that  
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**Factors Influencing Clinical Trial Site Selection in Europe:  
The Survey of Attitudes towards Trial sites in Europe  
(The SAT-EU Study<sup>TM</sup>)**

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Manuscripts

**Factors Influencing Clinical Trial Site Selection in Europe:**  
**The Survey of Attitudes towards Trial sites in Europe**  
**(The SAT-EU Study™)**

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**Study registration:** Posted on participating institution web site since September 22  
2011 (<http://www.sbg-marcom.ch/sat-eu.htm>)

**Key words:** Clinical trials; Clinical trial site selection criteria; European clinical trial  
competitiveness; European Clinical Trial Directive (CTD); European Health Policy

### Authors' contributions

MG: survey design and implementation; critical data analysis; manuscript drafting; overall project supervision

RT: survey design; statistical analysis; final manuscript editing

MM: survey design and implementation; survey advertising and data collection; critical data analysis; final manuscript editing

BC: survey design and implementation; survey advertising and data collection; critical data analysis; final manuscript editing

AP: survey design and implementation; survey advertising and data collection; critical data analysis; final manuscript editing

GG: survey design and implementation; critical data analysis; final manuscript editing

GA: survey design and implementation; critical data analysis; manuscript drafting; overall project supervision

### Data Sharing

Extra data is available in the form of raw survey data, providing individual (blinded) responses for each of 485 respondents. This data can be accessed either directly on the Survey Monkey platform or downloaded to excel from Survey Monkey. Our statistical analysis is also available upon request. Extra data is available by emailing [giuseppe.ambrosio@ospedale.perugia.it](mailto:giuseppe.ambrosio@ospedale.perugia.it)

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European Trial Site Selection Criteria - The SAT-EU Study™

Abstract (300 words)

**Objectives:** Applications to run clinical trials in Europe fell 25% between 2007 and 2011. Costs, speed of approvals, and shortcomings of European Clinical Trial Directive are commonly invoked to explain this unsatisfactory performance. However, no hard evidence is available on the actual weight of these factors, nor has it been previously investigated whether other criteria may also impact clinical trial site selection.

**Design:** The SAT-EU Study™ was an anonymous, cross-sectional Web-based survey that systematically assessed factors impacting European clinical trial site selection. It explored 19 factors across investigator-, hospital-, and environment-driven criteria, and costs. It also surveyed perceptions of the European trial environment.

**Setting and Participants:** Clinical Research Organizations (CROs), academic Clinical Trial Units (CTUs), and Industry invited to respond.

**Interventions:** None

**Outcome measures:** Primary: Weight assigned to each factor hypothesized to impact trial site selection and trial incidence; Secondary: Desirability of European countries to run clinical trials

**Results:** Responses were obtained from 485 professionals in 34 countries: 49% from BioPharma, 40% from CTUs or CROs. Investigator-, environment-, and hospital-dependent factors were rated highly important, costs being less important ( $P<0.0001$ ). Within environment-driven criteria, pool of eligible patients, speed of approvals, and presence of disease-management networks were significantly more important than costs or government financial incentives ( $P<0.0001$ ). The pattern of response was consistent across respondent groupings (CTU vs. CRO vs. Industry). Considerable variability was demonstrated in the perceived receptivity of countries to undertake clinical trials, with Germany, United Kingdom, and the Netherlands rated the best trial markets ( $P<0.0001$ ).

**Conclusions:** Investigator-dependent factors and ease of approval dominate trial site selection, while costs appear less important. Fostering competitiveness of European clinical research may not require additional government spending/incentives. Rather, harmonization of approval processes, greater visibility of centres of excellence, and reduction of “hidden” indirect costs, may bring significantly more clinical trials to Europe.

Article summary (292 words)

## Article focus

- Applications to perform clinical trials in the EU fell 25% from 2007 to 2011, with bureaucracy, the EU clinical trial directive 2001/20/EC, and costs reportedly to blame. Yet, the clinical research community lacks a systematic assessment of the relative weight of these and other criteria that may impact the viability of conducting clinical trials in Europe.
- The SAT-EU Study compiled the input of 485 decision makers to: (a) systematically evaluate 19 factors possibly impacting site selection for multicentre trials for which Europe is under consideration, and (b) to assess the relative desirability of doing trials in 12 European countries. The web-based survey was blinded and response choices were scrambled

## Key Messages

- Costs, and even more so government incentives, carry a surprisingly low weight, while investigator- and environment-dependent factors dominate trial site selection decisions
- Not previously highlighted is the fact that the viability of conducting trials in Europe is also a function of the availability of critical information to get centres recruited and trials started, such as via participation in Disease Area Networks and web research portals
- Germany, UK, and the Netherlands are seen as the best trial markets

## Strengths and Limitations

- *Strength:* We provide systematic evidence across a large sample of expert professionals indicating that fostering competitiveness of European clinical research may not require additional government spending/incentives. Carefully crafted harmonization of approvals, greater visibility of centres of excellence via disease networks/the web, and reduction of “hidden” costs are more likely to boost competitiveness of European clinical research
- *Limitations:* Consistent with voluntary surveys, we could only analyse responses provided by those interested in replying, and therefore cannot exclude that other points of view may have emerged from those who did not participate; our questionnaire may also have missed potentially important factors

## Introduction

Europe has consistently expressed a desire to maintain and improve clinical trial competitiveness,<sup>1-3</sup> most recently by advocating a “European Research Area” in which “researchers, scientific knowledge and technology circulate freely.”<sup>4</sup> A major component of the European governance for clinical research, European Clinical Trial Directive 2001/20/EC (CTD) was intended to support this goal, focussing on the harmonisation of research processes across EU member states.<sup>5-9</sup> However, the CTD failed to achieve its intended impact on the simplification and harmonization of administrative provisions governing clinical trials<sup>9</sup>, and thus on the level of European clinical research activity.<sup>2,10-11</sup> In fact, from 2007 to 2011, the number of clinical trial applications in Europe fell 25%<sup>12</sup>. Accordingly, although concerted calls for further CTD revisions continue<sup>13-14</sup> and recommendations awaiting member state review have been made by European Commission<sup>6</sup> and endorsed by scientific societies,<sup>15</sup> it is not clear which specific recommendations should be implemented or prioritized at either national or pan-European level.

Much of this uncertainty stems from insufficient understanding of the key drivers determining decision made by the healthcare industry, academic clinical trial units (CTUs), and clinical research organizations (CROs) in selecting European trial sites. Furthermore, although it is widely believed that costs and speed of approval are key factors influencing clinical trial incidence in Europe,<sup>6,16</sup> the relative weight of these and other important criteria is poorly understood. To our knowledge, no published studies have examined country and site selection criteria for trials conducted in Europe. Evidence is therefore needed to improve our understanding of stakeholders’ decision-making process.

The Survey of Attitudes towards Trial sites in Europe (The SAT-EU Study™) was established as a non-profit collaborative effort to systematically assess factors impacting clinical trial site selection in Europe. We also investigated whether trial

selection needs differ between academic and commercial sponsors. Finally, the survey sought to explore perceptions of the current European trial environment, and to identify areas for future improvement.

## Methods

### *Survey design*

The SAT-EU Study was an anonymous web-based cross-sectional survey undertaken between September 26<sup>th</sup> 2011, and January 21<sup>st</sup>, 2012. It included all stakeholder groups involved in clinical trial site selection, i.e., BioPharma companies, Medical Device manufacturers, CROs, and CTUs. The survey sought to capture information on both early- and late-phase studies. Late-phase studies were defined as phase III for CTUs, BioPharma and their sub-contractors (i.e., CROs), and phase IV for other participants (e.g. medical device companies).

A multi-stage approach was used to develop the survey. First, we identified the main criteria expected to impact site selection. Second, we organized these in four broad categories: (i) investigator-related, (ii) hospital/Institution-related, (iii) country/environment-related, and (iv) costs (evaluated both separately and within the environment category). Third, the defined criteria underwent review and discussion with a small number of knowledgeable professionals to ensure that potentially relevant criteria had not been missed (Figure 1).

The study group then built an internet-based survey hosted on a freely-accessible online questionnaire software (Survey Monkey, Palo Alto, CA, USA). Before launching the survey, healthcare market research experts (The Planning Shop International, London, UK) reviewed the survey design to optimize content and minimize bias. Additionally, a pilot survey undertaken by 15 respondents in June 2011 was used to validate and refine question content and organisation.

*Survey Procedure*

The survey consisted of 23 questions, which took some 20 minutes to complete. In sequence, questions asked participants to (1) provide demographic information anonymously (2) rate the importance of each of the hypothesized trial site selection criteria for Europe as a whole, (3) provide perception of the trial environment in 12 European countries, and (4) rank areas of potential improvement. Participants' feedback was assessed using a multiple-choice format, requiring respondents to provide a single response of rank. The full set of questions is accessible at [http://www.sbg-marcom.ch/sat-eu/Study\\_plan.html](http://www.sbg-marcom.ch/sat-eu/Study_plan.html). The order of presentation of individual responses to each question was scrambled across respondents to minimise response bias. At the end of each section, a response box allowed participants to provide open text comments, available as an "online supplement". Results of the survey were thoroughly reviewed among the study group, and subsequently discussed with a 25-member expert panel in Brussels on November 2012.

The survey was advertised through Industry and Clinical Trial Associations, online communities, social networks, and personal contacts of the SAT-EU Study group<sup>17</sup>, so that the precise number of people invited to participate is not known. No remuneration was provided to participants, but respondents were offered a summary of survey results once available.

*Statistical Analysis*

Given the descriptive nature of the SAT-EU study design, we did not formally estimate a required sample size. Instead, we sought to obtain at least 150 completed questionnaires from across the four stakeholder groups. Results are primarily presented descriptively as means (and 95% confidence intervals (95% CI)), or medians (and upper and lower quartiles), as appropriate to show results by group or country. Where data were available, responses were compared across three survey respondent

groupings (i.e. CTU vs. CRO vs. industry), and across responses within each survey question, using one-way analysis of variance.

## Results

A total of 485 individual responses were obtained, with participants providing responses to 72% of questions on average. Responders represented over 100 different institutions, including over 50 pharmaceutical, biotechnology or medical device firms, and over 20 CROs and CTUs.

### *Respondent Demographics*

Respondents represented over 37 countries, the top five contributors being Italy, USA, UK, Germany, and Spain (Table 1). Participants were almost evenly split between BioPharma (49%) and CROs/CTUs (40%) (Figure 2). In terms of hierarchy/job description, 43% were vice-president, director, or manager in a research or marketing position, and an additional 20% were head of a CTU (Figure 3, Left Panel). The majority of respondents described themselves as being directly involved in trial site selection decisions; almost two-thirds either personally headed, or sat on the trial site selection committee of their organization (Figure 3, Right Panel). Importantly, most respondents were the final decision makers, stating that they were either the “overall final decision maker”, or that trial site selection decisions were “entirely at (their) discretion”.

### *Relevance of investigator, environment, hospital, and costs criteria*

Respondents were asked to divide 100 points (reflecting their perceived level of importance) across four categories of factors impacting trial site selection. For both early- and late-phase trials (as defined in Methods), factors pertaining to the investigator, the hospital/unit, and the environment, were rated at a high level of

importance (25 or above) (Table 2). When combined, investigator- and hospital-dependent levers were reported to be instrumental in trial site choice for both early- and late-phase studies (average weight 60/100 and 57/100 respectively). In contrast, cost factors were considered to be less important for both early- and late-trials ( $P<0.0001$ ) (Table 2). This pattern of response was consistent across survey respondent groupings (i.e. CTU vs. CRO vs. industry; not shown).

*Investigator-Driven Criteria*

Respondents were asked to assign 100 points across five investigator-related criteria. There was a statistically significant difference in the level of importance of the factors tested, with investigator track record in prior trials, experience in similar studies, and interest in study scoring a level of importance of 20 or above, while concurrent trial workload, and publication track record were significantly less important ( $P<0.0001$ ) (Table 3). The pattern of response was again consistent across survey respondent groupings (not shown).

*Environment-Driven Criteria*

To explore environmental dynamics, respondents were asked to assign 100 points across six environment-related criteria. Market size/pool of eligible patients in the region, speed of approvals, and presence of disease management networks, were assigned a greater level of importance. In contrast, costs of running trials, and particularly government financial/tax incentives were considered to be of significantly lower importance ( $P<0.0001$ ) (Table 4). Also in this case, the pattern of response was consistent across survey respondent groupings (not shown).

*Hospital-Driven Criteria*

In this domain, 100 points had to be assigned across six criteria that explored characteristics of the specific hospital/unit where a clinical trial may potentially be run. There was a statistically significant difference in the level of importance of hospital-

driven criteria, whereby site personnel experience and training, respondent's previous experience with site, and availability of facilities and equipment required by trial scored above 20 ( $P < 0.0001$ ). In contrast, site personnel language capabilities and hospital quality assurance process were significantly less important (Table 5).

### *Perception of European Trial Environment*

Our survey showed a statistically significant difference in respondents' perceived desirability of running clinical trials across the twelve EU countries tested, i.e., Europe's top 5 healthcare markets (Germany, France, Italy, the UK, and Spain), large east European markets (Poland, Hungary, Czech Republic), plus Netherlands, Belgium, Switzerland, and Austria. For both accessibility and transparency of all information required to run clinical trials (Figure 4, Upper Panel), and availability of equipment (not shown), Germany, UK and the Netherlands were the top three scorers. With regard to predictability and speed of Ethics Committees, Belgium was the top scorer, followed by Germany and the Netherlands (Figure 4, Lower Panel). In terms of overall trial site "desirability", respondents scored Germany as the most desirable trial location, followed by the Netherlands and UK ( $P = 0.0001$ ) (Figure 5).

### *Possible Improvements*

Two questions tested the hypothesis that making a site more visible would be desirable from the decision-makers' perspective. We found that 83% of respondents would have been "much more likely" to include a site if all relevant investigator- and hospital-related information were readily available (Figure 6, Left Panel). Furthermore, 75% believed that web-site information would be either "definitely welcome", or "useful most of the time" (Figure 6, Right Panel).

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## Discussion

The SAT-EU Study<sup>TM</sup> was a web-based survey designed to identify perceived drivers and hurdles associated with conducting clinical trials in Europe. We obtained responses from over four hundred participants in key stakeholder groups, i.e. BioPharma industry, medical device manufacturers, CROs, and CTUs. The vast majority of countries actively involved in clinical trials were represented, while most respondents were key decision makers in their organizations. These features allowed us to get direct and potentially relevant insights into the reasoning behind site selection for clinical trials.

Recent years have seen much public policy discussion on the need to foster Europe's role in medical research, and to rekindle its dwindling attractiveness for investment in clinical trials.<sup>18-20</sup> Various strategies have been proposed based on a "common sense" approach. Whilst possibly sound, policy recommendations were typically not founded on a systematic understanding of factors impacting clinical trial site selection. Indeed, one could argue that, borrowing from the rigour of its own discipline, medical policy decisions at all levels ought to be "evidence-based". Regretfully however, this approach seems to be largely absent. To our knowledge, the SAT-EU study is the first effort aimed at systematically investigating factors impacting trial site attractiveness across Europe. Given the survey's size, the variety of domains explored, the number of countries and organizations involved, and the prevalence of senior decision makers, our results may provide insight into "real world" trial site decisions.

Our study has several key findings. First, there was evidence of considerable variability in the perceived receptivity of European countries to undertake clinical trials, Germany, United Kingdom, and the Netherlands being rated the best markets. Reasons for greater appeal of certain countries are multiple. Larger countries could be

more attractive because of greater patient recruitment potential, and in prospect, because of the size of their markets. However, country size does not entirely explain the phenomenon, given the excellent results of small countries such as the Netherlands, and the low score of large countries such as Italy or Spain. Our survey sheds some light on this by pointing to the negative impact of administrative burden on clinical trial competitiveness. This is not only a concern at country level. Central to this discussion is the notion that the time required to collect information to determine a site's feasibility for inclusion in a trial, and to get it started, is also critical. Hence, the high weight placed on a site's proven track record in efficiently delivering results, which bears a relationship to specialized clinical research centres, and equally important, to the ability of clinical trial sponsors and organizers to access all of the required information quickly and effectively. Accordingly, the downsides of operating within a sub-optimal regulatory environment may not prejudice selection of an otherwise visible and competent investigator, whose trial site information is readily available and who is able to recruit the required patients. A third important finding of our survey is that contrary to a widely held tenet, costs of running trials - often invoked to explain why industry is going outside Europe<sup>6,16</sup> - as well as government incentives/tax breaks, are not the main considerations when selecting European sites. In other words, it would seem from stakeholders' feedback and follow-up discussions that to the extent that European centers may be excluded from a trial, the likely culprit is the hidden costs associated with excessive administrative time required to get a trial site up and running, not the high fees per enrolled patient. Although apparently surprising, the limited impact of costs needs to be considered against the backdrop of the various issues to which our survey tried to provide a response. Indeed, in addition to "direct" costs, a major negative factor is represented by indirect, or "hidden" costs, such as those characterized by time lost through layers of bureaucracy, slow recruitment by sites, or poor overall site performance. Hence, the importance of not only bureaucracy,

but also of the level of training and trial expertise at sites. Additionally, the notion that investments in clinical trials in Europe cannot be easily improved through government incentives or tax breaks may have important implications in terms of public policy. Comments obtained through our survey seem to indicate that stakeholders would like a single European “trial market” allowing them to gear trial site selection to expert investigators and to optimal patient recruitment, unobstructed by heterogeneous regulations or hurdles to obtaining crucial information. Participants expressed this need in two main ways. First, from a regulatory or “macro” perspective, they expressed desire for easier approval processes with less national variability and stronger pan-European element. This may indicate ethical committee approval timeframes, as well as institutional approvals at site level. Second, from a clinical research or “micro” perspective, respondents want access to transnational networks of disease-area experts, through visibility of experienced trial units via the internet and/or via participation in disease networks.

More than 50 years ago, the founders of the European Union envisioned a single market at the core of the European project. Despite this, a “single market” vision for clinical research did not develop as envisaged. This is damaging to an industry in which much of the investment in clinical trials is by necessity multinational. Indeed, Europe’s 2020 growth strategy calls for 3% of its Gross National Product to be invested in research and development (R&D) by 2020<sup>21</sup>. If this goal is to be achieved, BioPharma - the European sector with the highest R&D/Sales ratio<sup>22</sup> - should be allowed to invest in Europe without facing unnecessary roadblocks. Given the size of its healthcare market, its aging population, its well-established pharmaceutical industry, and the quality of its research centres and investigators, Europe has a formidable comparative advantage in clinical research. Individual European member states are well poised to take advantage of this by making the EU more competitive in clinical research. They should be encouraged to do so, not simply by investing in incentives or

tax breaks, but by implementing revisions to the CTD that are under consideration by member states, and by legislating removal of unhelpful bureaucratic barriers at national level. Improving hospital contracting, such as via national or even pan-European contract templates, would also significantly reduce administrative burden, speed up trial start, and make the European landscape significantly more competitive. On their part, the research community and relevant national bodies have a parallel imperative to ensure that hospitals and institutions are organised and networked more effectively, and that there is adequate training of trial staff. They need to ensure that clinical centres wishing to undertake more research are made more visible to industry and to international research communities, through dedicated research portals on their web sites, or by creating and/or joining disease networks. Finally, given that selected countries are consistently scored above others, a best practice audit of administrative provisions governing and supporting clinical trials in countries such as Germany, the UK, the Netherlands<sup>14</sup> would be helpful for drawing policy implications for other countries. The case for action rests on the realization that evidence-based policy is indeed possible in this arena. Learning from what is working successfully will facilitate the road to creating a more welcoming environment for clinical research in Europe.

**Limitations**

Consistent with voluntary surveys, we could only analyse responses provided by those who were interested in replying, and therefore we cannot exclude that other points of view may have emerged from those who did not participate. Nonetheless, it is rather reassuring that the responses were gathered through a fairly large number of professionals who belonged to a variety of organizations from a number of countries, and who were for the most part the final decision makers in the process. However, given that participation was largely through professional bodies and web-based communities, we are unable to provide an estimate of our coverage. . Whilst we took

care in designing a survey that focused on the key determinants of trial site selection, we may have missed potentially important issues. We tried to minimize this through preliminary survey review and refinement with the help of external experts. In addition,, some of our questions in relation to process and speed of approval may need further research to determine the root issues, as problems differ from country to country, and have to be weighed against the need to ensure that patient safety remains unprejudiced.

## Conclusions

Our study indicates that fostering European clinical research and attracting more trials to Europe does not require additional government spending. Instead, we believe our findings support a more harmonised national adoption of the clinical trial approvals process, greater visibility of transnational networks of disease experts, and greater accessibility to research system at national and pan-European levels. Potential models for improvement include harmonization of ethical and institutional approvals systems, including aligned hospital contracting and greater visibility of centres of excellence, which may bring significantly more clinical research to Europe. Europe needs growth, and clinical research can play its part in directly stimulating economic activity while simultaneously boosting European innovation.

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<http://www.appliedclinicaltrials.com/>

European Forum for Good Clinical Practice (EFGCP)

<http://www.efgcp.be>

European Federation of Pharmaceutical Industry Associations (EFPIA)

<http://www.efpia.eu/>

European Biotech Industry Association (EuropaBio)

<http://www.europabio.org/>

Perugia University, Italy

<http://facolta.unipg.it/medicina/>

Drug Information Association (DIA)

<http://www.diahome.org/DIAHome/Home.aspx>

Virtuoso Consulting, Geneva, Switzerland

<http://www.virtuoso.ch/model.html>

European Vision Institute Clinical Research Network (Disease Network)

<http://www.evicr.net>

EUCOMED Clinical Trial Interest Group

<http://www.eucomed.be/>

Pharma IQ

<http://www.pharma-iq.com/>

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## Competing Interests

All co-authors work in the area of healthcare, either academia or consulting, and as such have all been, or are involved in, the initiation, execution or interpretation of clinical trials. Accordingly, all co-authors have an intellectual/academic interest in seeing the European Clinical trial industry enhance its competitiveness. None of the authors however, stands to gain any more than any other member of the European healthcare community from the implementation of any of the recommendations made in the manuscript. We declare no other conflict of interest, and no other relationships or activities that could appear to have influenced the submitted work.

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## Table and Figure Legend

### Table 1: Respondent work location

### Table 2: Levers impacting trial site selection for early and late trials

Respondents were asked to divide 100 points across the below 4 levers impacting their trial site selection for early phase studies:

(Pharma, Biotech, CROs, CTUs, answer for phase II studies)

(Medical device and all others answer for phase III studies)

and then for later phase studies:

(Pharma, Biotech, CROs, CTUs, answer for phase III studies)

(Medical device and all others answer for phase IV studies)

Bars represent mean and 95% Confidence Interval (N=341)

There was evidence of a statistically significant difference in the level of importance among the 4 factors ( $P < 0.0001$ )

### Table 3: Investigator-driven criteria in selection of trial sites of phase II–III study sites (phase III–IV for medical devices)

Respondents were asked to rate investigator-driven criteria by dividing 100 points across 5 criteria potentially relevant in selecting trial sites for phase III studies:

(Pharma, Biotech, CROs, CTUs, answer for phase III studies)

(Medical device and all others answer for phase IV)

Bars represent mean and 95% Confidence Interval (N=341)

There was evidence of a statistically significant difference in the level of importance among the 5 criteria ( $P < 0.0001$ )

### Table 4: Environment-driven criteria in selection of trial sites of phase II–III study sites (phase III–IV for medical devices)

Respondents were asked to rate environment-driven criteria by dividing 100 points across 6 criteria potentially relevant in selecting trial sites for phase III studies:

(Pharma, Biotech, CROs, CTUs, answer for phase III studies)

(Medical device and all others answer for phase IV)

Bars represent mean and 95% Confidence Interval (N=341)

There was evidence of a statistically significant difference in the level of importance among the 6 criteria ( $P < 0.0001$ )

### Table 5: Hospital-driven criteria in selection of phase II–III study sites (phase III–IV for medical devices)

Respondents were asked to rate Hospital driven criteria by dividing 100 points across 6 criteria potentially relevant in selecting trial sites for phase III studies:

(Pharma, Biotech, CROs, CTUs, answer for phase III studies)

(Medical device and all others answer for phase IV)

Bars represent mean and 95% Confidence Interval (N=342)

There was evidence of a statistically significant difference in the level of importance among the 6 criteria ( $P < 0.0001$ )

**Figure 1: Hypothesis about trial site selection criteria**

Four categories of levers potentially impacting trial site selection were identified. Survey weighed relevance across these four levers, then drilled down for weight within each sub-category.

**Figure 2: Respondent's Organization**

Respondents were asked to answer the question: "Please indicate which organisation most closely resembles yours"

Bars show percent distribution of 485 individual responses

**Abbreviations**

- Pharma = Industry: Pharmaceutical Company
  - CRO = Clinical Research Organisation
  - CTU = Academic Clinical Trial Unit
  - Biotech = Industry: Biotechnology Company
- Medical Devices included: Medical Devices, Radiological, Electro-medical or HealthCare Information Technology

"Other" included following self-reported categories:

- Respondent working for a mixed portfolio industry with either Pharma/Biotech portfolio or Pharm/Medical Device portfolio (self reported)
- Regulatory/Clinical Consultant
- Hospital or private clinic

**Figure 3**

**Left Panel: Respondent hierarchy**

Respondents were asked to answer the question: "Please indicate the position which most closely resembles yours"

Chart shows percent distribution of 485 individual responses

VP = Vice President

"Others" were respondents who wanted to be more specific in their titles:

- Global Study Manager/Clinical Research Associate
- Regulatory Affairs/ Regulatory in a Clinical department/ Good Clinical Practice Quality Assurance Manager, or Director/ Safety Pharmacovigilance Officer
- Medical Affairs/ Medical Director/Clinical Director/Global Scientific Affairs
- General Manager
- "Professor or Lecturer"

**Right Panel: Respondent organisation's decision-making process**

Respondents were asked to answer the question: "Please indicate which most closely resembles how trial site selection decisions are made at your institution"

Chart shows percent distribution of 485 individual responses

Other included:

- My staff decides

- Decision outsourced to CRO
- CRA decides
- Decisions according to Standard Operation Procedures
- Many people involved in decision, or Study Team decides
- Our affiliates decide

#### Figure 4

##### Upper Panel

##### **Accessibility and transparency of all types of information required to make trial site selection decisions - Twelve country rank (N=296)**

Respondents were asked to rate twelve countries for the accessibility and transparency of information (of all types) required to make trial site selection  
Bars represent mean and 95% Confidence Interval

Statistically significant difference in satisfaction across EU countries ( $P = 0.0001$ )

##### Lower Panel

##### **Predictability and speed of Ethics Committees and IRBs for phase II-III multi-centre RCTs - Twelve country rank (N=296)**

Respondents were asked to rate twelve countries for the speed of their ethics committees & IRBs for phase III (3) multi centric RCTs  
Bars represent mean and 95% Confidence Interval (number of respondents in parentheses)

Statistically significant difference in satisfaction across EU countries ( $P = 0.0001$ )  
IRB = institutional review board

#### Figure 5: Trial Site Desirability by country

##### Trial Site Desirability "Index" - Nine Country Rank

Respondents were asked to provide their "personal perception" ranking of the desirability of running trials in 9 countries, ranking them from (1) "most desirable" country to (9) "least desirable" country (if needed, they could click "no opinion" in up to three countries they know the least)  
Data are presented as whisker-box plot of median and lower and upper quartile

There was evidence of a statistically significant difference in the perceived desirability of running trials across EU countries ( $P = 0.0001$ )

**Figure 6**  
**Left Panel: Likelihood of selecting trial site given relevant information**

Respondents were asked to rate their level of agreement with the statement:  
“I am much more likely to select a trial site if I have all of the relevant Investigator and Site specific information easily available to me”  
Chart represents percent response (N=253)

**Right Panel: Usefulness of trial site web site information**

Respondents were asked to pick the statement that they felt closest to with reference to the assertion that “it would be useful to have relevant trial information readily visible in a dedicated public section the Hospital's web site (Facilities, equipment, personnel qualification, Ethics Committee and Institutional Review Board timings, contact people for trials, etc.)

**Table 1: Respondent work location (N=485)**

Country	Respondents
Australia	1
Austria	4
Belgium	21
Brazil	1
Bulgaria	3
Canada	6
China	1
Croatia	1
Czech Republic	1
Denmark	21
Egypt	1
Estonia	1
Finland	11
France	21
Germany	46
Greece	4
Hungary	4
India	13
Ireland	8
Israel	5
Italy	75
Netherlands	16
Nigeria	1
Norway	1
Poland	7
Portugal	9
Romania	7
Russia	1
Serbia	1
Slovakia	1
Slovenia	2
Spain	44
Sweden	13
Switzerland	20
Ukraine	1
United Kingdom	48
USA	58
Not Available	6

Table 2 Levers impacting trial site selection for early and late trials						
Lever	Response Mean		Upper 95% Confidence Limit (U95CL)		Lower 95% Confidence Limit (U95CL)	
	Early Phase	Late Phase	Early Phase	Late Phase	Early Phase	Late Phase
Investigator factors	30.2	29.1	31.5	30.4	28.9	27.8
Hospital/unit factors	28.4	28.3	29.7	29.7	27.0	26.9
Environmental factors	25.5	23.5	26.6	24.7	24.3	22.4
Cost factors	16.0	19.0	17.2	20.4	14.7	17.7

Legend for Table 2

Respondents (N=341) were asked to divide 100 points across the above 4 levers impacting their trial site selection for early phase studies:

- Pharma, Biotech, CROs, CTUs, answered for phase II (2) studies
- Medical device and all others answered for phase III (3) studies

Then respondents were asked to do the same as above for later phase studies:

- Pharma, Biotech, CROs, CTUs, answered for phase III (3) studies
- Medical device and all others answered for phase IV (4) studies

There was evidence of a statistically significant difference in the level of importance of the 4 factors ( $P < 0.0001$ )

The pattern of response (not shown here) appeared to be consistent across survey respondent groupings (i.e. CTU vs. CRO vs. industry)

**Table 3**

Investigator-driven criteria in selection of phase II-III trial sites  
(Phase III-IV for medical device)

Criteria	Mean	Upper 95% Confidence Limit (U95CL)	Lower 95% Confidence Limit (U95CL)	Standard Deviation
Investigator recruitment/retention track record	27.3	28.5	22.4	13.3
Investigator experience in previous trials	22.7	23.8	21.6	12.0
Investigator interest	22.42	23.6	21.3	13.4
Investigator concurrent workload	17.2	18.2	16.2	9.8
Investigator publication track record	10.4	11.3	9.6	10.9

**Legend for Table 3:**

Respondents (N=341) were asked to divide 100 points across the above 5 criteria when selecting trial sites for phase III/IV (3/4) studies:

- Pharma, Biotech, CROs, CTUs answered for phase III (3) studies
- Medical device and all others answered for phase IV (4) studies

There was evidence of a statistically significant difference in the level of importance of the 5 criteria ( $P < 0.0001$ )

The pattern of response (not shown here) appeared to be consistent across survey respondent groupings (i.e. CTU vs. CRO vs. industry)

<b>Table 4</b> Environment-driven criteria in selection of phase II-II trial sites (Phase III-IV for medical devices)				
Criteria	Average	Upper 95% Confidence Limit (U95CL)	Lower 95% Confidence Limit (U95CL)	Standard Deviation
Size of market/eligible patients in region	23.8	25.2	22.4	13.3
Speed of MoH/Ethics Committees approval	23.4	24.6	22.1	12.0
Disease management system/networks	18.9	20.4	17.5	13.4
Cost of running trial	15.2	16.3	14.2	9.8
Presence of country on "core country list"	11.8	13.0	10.7	10.9
Government financial/tax incentives	6.9	7.6	6.2	6.6

**Legend for Table 4**

Respondents (N=341) were asked to divide 100 points across the above 6 criteria when selecting trial sites for phase III/ IV (3/4) studies:

- Pharma, Biotech, CROs, CTUs answered for phase III (3) studies
- Medical device and all others answered for phase IV (4) studies

There was evidence of a statistically significant difference in the level of importance of the 6 criteria (P < 0.0001)

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<b>Table 5</b> <b>Hospital-driven criteria in selection of phase II-III trial sites</b> <b>(Phase III-IV for medical devices)</b>			
	Average	Upper 95% Confidence Limit (U95CL)	Lower 95% Confidence Limit (U95CL)
Site personnel experience and training	22.0	23.1	20.84
Previous experience with site	20.0	21.2	18.7
Facilities/equipment required by trial	19.7	20.7	18.7
Hospital approval/contracting system	17.4	18.5	16.4
Site personnel language proficiency	10.8	11.7	10.0
Hospital Quality Assurance process	10.1	10.9	9.2

**Legend for Table 5:**

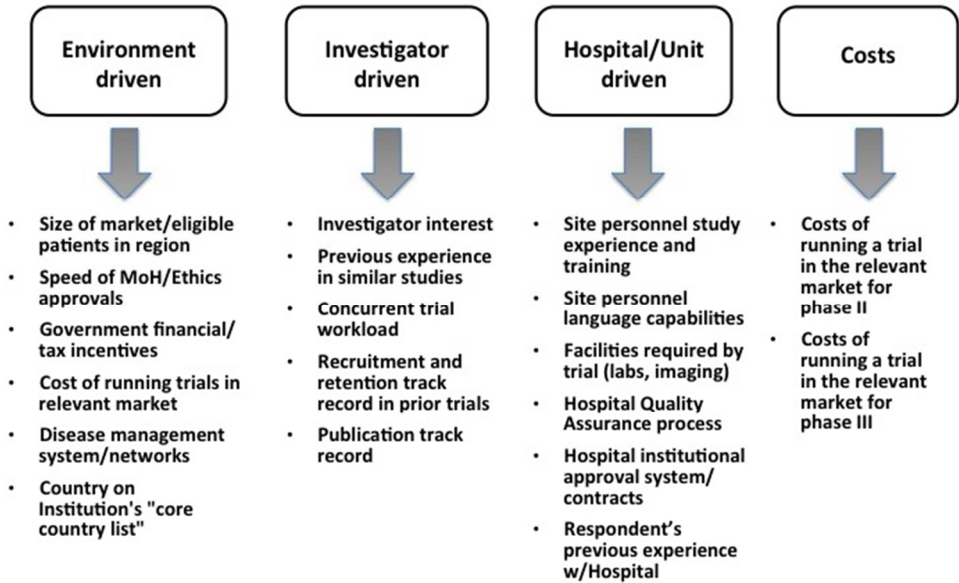
Respondents (N=341) were asked to rate Hospital driven criteria by dividing 100 points across 6 criteria potentially used when selecting trial sites for phase III studies:

- Pharma, Biotech, CROs, CTUs, answer for phase III studies
- Medical device and all others answer for phase IV

There was evidence of a statistically significant difference in the level of importance of the 6 criteria (P < 0.0001)

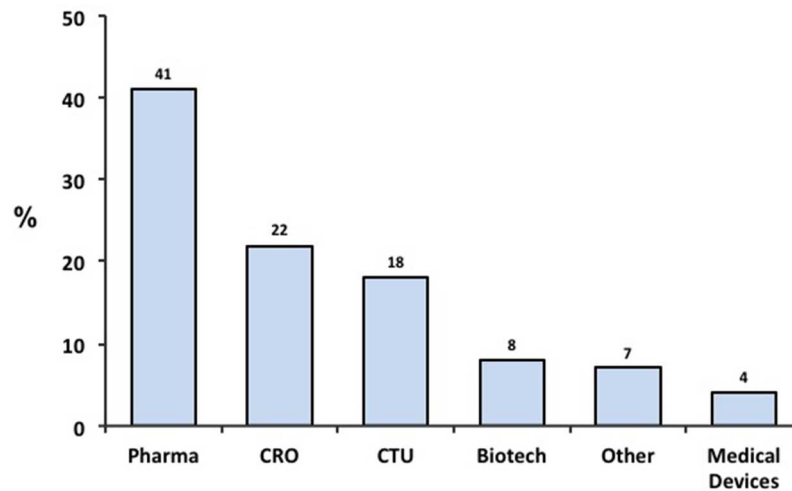
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Figure 1  
Hypothesis about trial site selection criteria



Hypothesis about trial site selection criteria  
Four categories of levers potentially impacting trial site selection were identified.  
Survey weighed relevance across these four levers, then drilled down for weight within each sub-category  
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*Figure 2*  
**Respondents' Organisation**

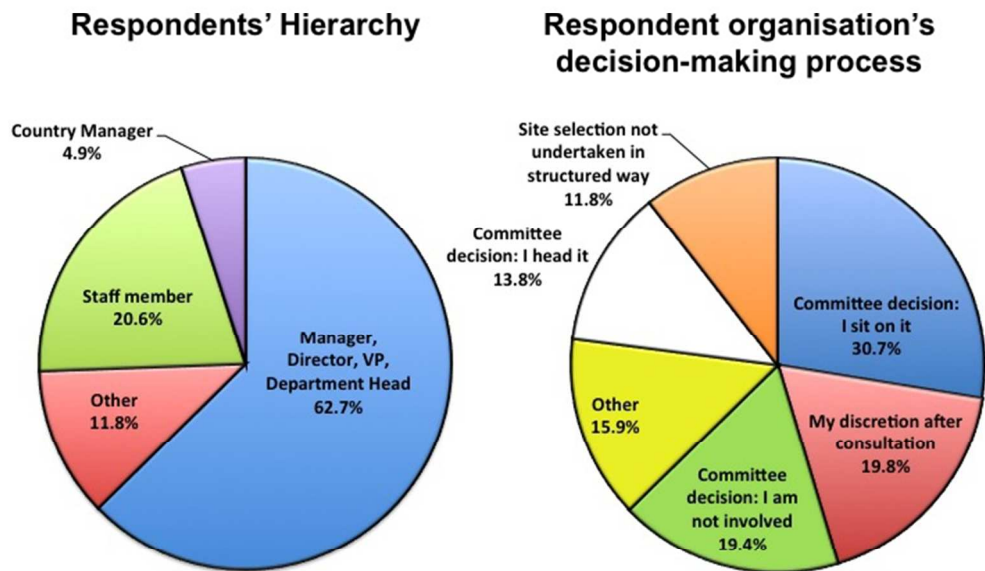


Respondent's Organization

Respondents were asked to answer the question: "Please indicate which organisation most closely resembles yours"

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Figure 3



Left Panel: Respondent hierarchy  
Respondents were asked to answer the question: "Please indicate the position which most closely resembles yours"

Chart shows percent distribution of 485 individual responses  
VP = Vice President  
"Others" were respondents who wanted to be more specific in their titles:  
– Global Study Manager/Clinical Research Associate  
– Regulatory Affairs/ Regulatory in a Clinical department/ Good Clinical Practice Quality Assurance Manager, or Director/ Safety Pharmacovigilance Officer  
– Medical Affairs/ Medical Director/Clinical Director/Global Scientific Affairs  
– General Manager  
– "Professor or Lecturer"

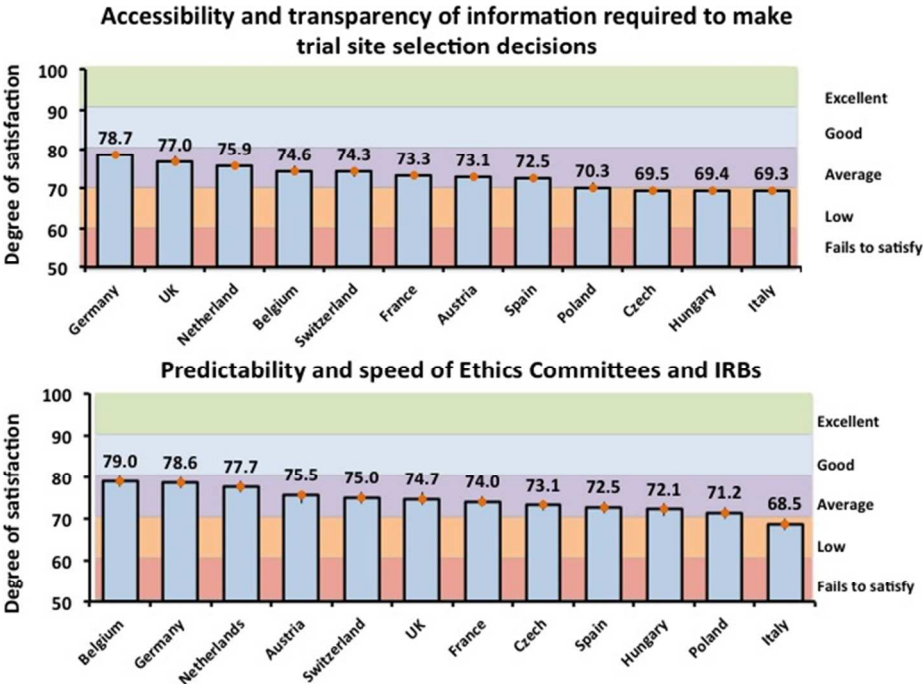
Right Panel: Respondent organisation's decision-making process  
Respondents were asked to answer the question: "Please indicate which most closely resembles how trial site selection decisions are made at your institution"

Chart shows percent distribution of 485 individual responses  
Other included:  
– My staff decides  
– Decision outsourced to CRO  
– CRA decides  
– Decisions according to Standard Operation Procedures  
– Many people involved in decision, or Study Team decides  
– Our affiliates decide

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Figure 4



Upper Panel

Accessibility and transparency of all types of information required to make trial site selection decisions - Twelve country rank (N=296)  
Respondents were asked to rate twelve countries for the accessibility and transparency of information (of all types) required to make trial site selection  
Bars represent mean and 95% Confidence Interval

Statistically significant difference in satisfaction across EU countries (P = 0.0001)

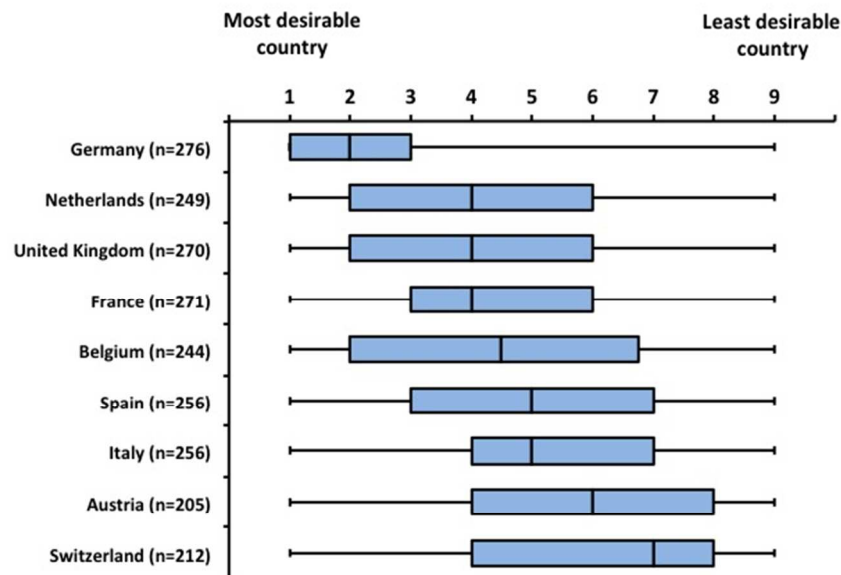
Lower Panel

Predictability and speed of Ethics Committees and IRBs for phase II-III multi-centre RCTs - Twelve country rank (N=296)  
Respondents were asked to rate twelve countries for the speed of their ethics committees & IRBs for phase III (3) multi centric RCTs  
Bars represent mean and 95% Confidence Interval (number of respondents in parentheses)

Statistically significant difference in satisfaction across EU countries (P = 0.0001)

IRB = institutional review board  
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**Figure 5**  
**Trial Site Desirability by Country**



Trial Site Desirability by country

Trial Site Desirability "Index" - Nine Country Rank

Respondents were asked to provide their "personal perception" ranking of the desirability of running trials in 9 countries, ranking them from (1) "most desirable" country to (9) "least desirable" country (if needed, they could click "no opinion" in up to three countries they know the least)

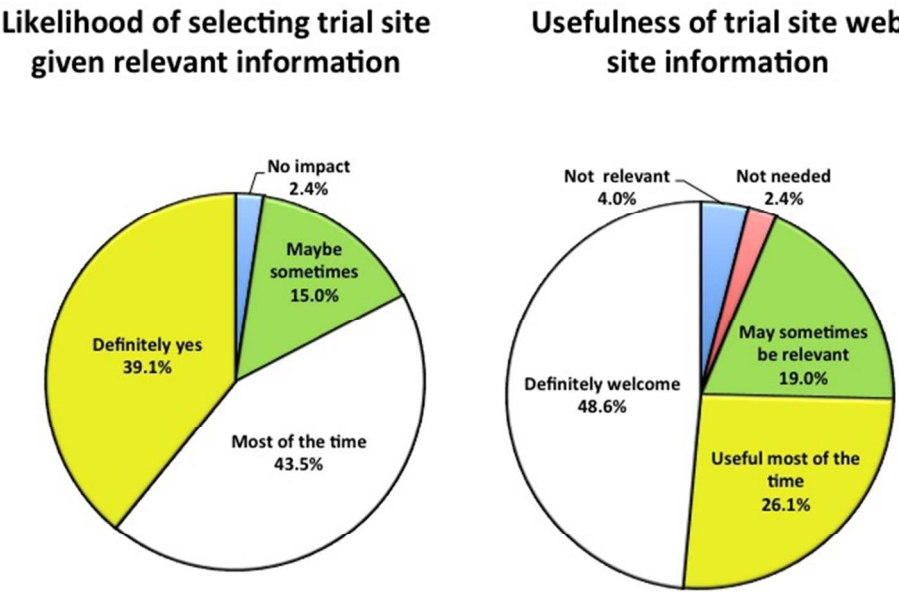
Data are presented as whisker-box plot of median and lower and upper quartile

There was evidence of a statistically significant difference in the perceived desirability of running trials across EU countries ( $P = 0.0001$ )

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Figure 6



Left Panel: Likelihood of selecting trial site given relevant information  
Respondents were asked to rate their level of agreement with the statement:  
"I am much more likely to select a trial site if I have all of the relevant Investigator and Site specific information easily available to me"  
Chart represents percent response (N=253)

Right Panel: Usefulness of trial site web site information  
Respondents were asked to pick the statement that they felt closest to with reference to the assertion that  
"it would be useful to have relevant trial information readily visible in a dedicated public section the Hospital's web site (Facilities, equipment, personnel qualification, Ethics Committee and Institutional Review Board timings, contact people for trials, etc.)"

254x190mm (72 x 72 DPI)

European Trial Site Selection Criteria - The SAT-EU Study<sup>TM</sup>  
July 31st 2013

## Factors Influencing Clinical Trial Site Selection in Europe: The Survey of Attitudes towards Trial sites in Europe (The SAT-EU Study<sup>TM</sup>)

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| Word count for Abstract: ~~300299~~

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2011 (<http://www.sbg-marcom.ch/sat-eu.htm>)

**Key words:** Clinical trials; Clinical trial site selection criteria; European clinical trial  
competitiveness; European Clinical Trial Directive (CTD); European Health Policy

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**Authors' contributions**

MG: survey design and implementation; critical data analysis; manuscript drafting; overall project supervision  
RT: survey design; statistical analysis; final manuscript editing  
MM: survey design and implementation; survey advertising and data collection; critical data analysis; final manuscript editing  
BC: survey design and implementation; survey advertising and data collection; critical data analysis; final manuscript editing  
AP: survey design and implementation; survey advertising and data collection; critical data analysis; final manuscript editing  
GG: survey design and implementation; critical data analysis; final manuscript editing  
GA: survey design and implementation; critical data analysis; manuscript drafting; overall project supervision

**Data Sharing**

Extra data is available in the form of raw survey data, providing individual (blinded) responses for each of 485 respondents. This data can be accessed either directly on the Survey Monkey platform or downloaded to excel from Survey Monkey. Our statistical analysis is also available upon request. Extra data is available by emailing [giuseppe.ambrosio@ospedale.perugia.it](mailto:giuseppe.ambrosio@ospedale.perugia.it)

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## European Trial Site Selection Criteria - The SAT-EU Study™

### Abstract (300299 words)

**Objectives:** Applications to run clinical trials in Europe fell 25% between 2007 and 2011. Costs, speed of approvals, and shortcomings of European Clinical Trial Directive are commonly invoked to explain this unsatisfactory performance. However, no hard evidence is available on the actual weight of these factors, nor it has it been previously investigated whether. Furthermore, the possibility that other criteria may also impact clinical trial site selection has never been investigated.

**Design:** The SAT-EU Study™ was an anonymous, cross-sectional Web-based survey that systematically assessed factors impacting European clinical trial site selection. It explored 19 factors across investigator-, hospital-, and environment-driven criteria, and costs. It also surveyed perceptions of the European trial environment.

**Setting and Participants:** Clinical Research Organizations (CROs), academic Clinical Trial Units (CTUs), and Industry invited to respond.

**Participants:** ~~Responses obtained from 485 professionals in 34 countries: 49% from BioPharma, 40% from CTUs or CROs.~~

**Interventions:** None

**Outcome measures:** Primary: Weight assigned to each factor hypothesized to impact trial site selection and trial incidence; Secondary: Desirability of European countries to run clinical trials

**Results:** Responses were obtained from 485 professionals in 34 countries: 49% from BioPharma, 40% from CTUs or CROs. Investigator-, environment-, and hospital-dependent factors were rated highly important, costs being less important ( $P < 0.0001$ ). Within environment-driven criteria, pool of eligible patients, speed of approvals, and presence of disease-management networks were significantly more important than costs or government financial incentives ( $P < 0.0001$ ). The pattern of response was consistent across respondent groupings (CTU vs. CRO vs. Industry). Considerable variability was demonstrated in the perceived receptivity of countries to undertake clinical trials, with Germany, United Kingdom, and the Netherlands rated the best trial markets ( $P < 0.0001$ ).

**Conclusions:** Investigator-dependent factors and ease of approval dominate trial site selection, while costs appear less important. Fostering competitiveness of European clinical research may not require additional government spending/incentives. Rather, carefully crafted harmonization of approvals processes, greater visibility of centres of excellence, and reduction of "hidden" indirect costs, may bring significantly more clinical trials to Europe.

Article summary (2929 words)

Article focus

- Applications to perform clinical trials in the EU fell 25% from 2007 to 2011, with bureaucracy, the EU clinical trial directive 2001/20/EC, and costs reportedly to blame. Yet, the clinical research community lacks a systematic assessment of the relative weight of these and other criteria that may impact the viability of conducting clinical trials in Europe.
- The SAT-EU Study compiled the input of 485 decision makers to: (a) systematically evaluate 19 factors possibly impacting site selection for multicentre trials for which Europe is under consideration, and (b) to assess the relative desirability of doing trials in 12 European countries. The web-based survey was blinded and response choices were scrambled

Key Messages

- Costs, and even more so government incentives, carry a surprisingly low weight, while a number of investigator- and environment-dependent factors dominate trial site selection decisions
- Not previously highlighted is the fact that the viability of conducting trials in Europe is also a function of the availability of critical information to get centres recruited and trials started, such as via participation in Disease Area Networks and web research portals
- Germany, UK, and the Netherlands are seen as the best trial markets

Strengths and Limitations

- *Strength:* We provide systematic evidence across a large sample of expert professionals indicating that fostering competitiveness of European clinical research may not require additional government spending/incentives. We deliver convincing evidence to demonstrate that carefully crafted harmonization of approvals, greater visibility of centres of excellence via disease networks/the web, and reduction of “hidden” costs are more likely to boost competitiveness of European clinical research
- *Limitations:* Consistent with voluntary surveys, we could only analyse responses provided by those interested in replying, and therefore cannot exclude that other points of view may have emerged from those who did not participate; our questionnaire may also have missed potentially important factors

## Introduction

Europe has consistently expressed a desire to maintain and improve clinical trial competitiveness,<sup>1-3</sup> most recently by advocating a “European Research Area” in which “researchers, scientific knowledge and technology circulate freely.”<sup>4</sup> A major component of the European governance for clinical research, European Clinical Trial Directive 2001/20/EC (CTD) was intended to support this goal, focussing on the harmonisation of research processes across EU member states.<sup>5-9</sup> However, the CTD failed to achieve its intended impact on the simplification and harmonization of administrative provisions governing clinical trials<sup>9</sup>, and thus on the level of European clinical research activity.<sup>2,10-11</sup> In fact, from 2007 to 2011, the number of clinical trial applications in Europe fell 25%<sup>12</sup>. Accordingly, although concerted calls for further CTD revisions continue<sup>13-14</sup> and recommendations awaiting member state review have been made by European Commission<sup>6</sup> and endorsed by scientific societies,<sup>15</sup> it is not clear which specific recommendations should be implemented or prioritized at either national or pan-European level.

Much of this uncertainty stems from insufficient understanding of the key drivers determining decision made by the healthcare industry, academic clinical trial units (CTUs), and clinical research organizations (CROs) in selecting European trial sites. Furthermore, although it is widely believed that costs and speed of approval are key factors influencing clinical trial incidence in Europe,<sup>6,16</sup> the relative weight of these and other important criteria is poorly understood. To our knowledge, no published studies have examined country and site selection criteria for trials conducted in Europe. Evidence is therefore needed to improve our understanding of stakeholders’ decision-

making process.

The Survey of Attitudes towards Trial sites in Europe (The SAT-EU Study™) was established as a non-profit collaborative effort to systematically assess factors impacting clinical trial site selection in Europe. We also investigated whether trial selection needs differ between academic and commercial sponsors. Finally, the survey sought to explore perceptions of the current European trial environment, and to identify areas for future improvement.

**Methods**

*Survey design*

The SAT-EU Study was an anonymous web-based cross-sectional survey undertaken between September 26<sup>th</sup> 2011, and January 21<sup>st</sup>, 2012. It included all stakeholder groups involved in clinical trial site selection, i.e., BioPharma companies, Medical Device manufacturers, CROs, and CTUs. The survey sought to capture information on both early- and late-phase studies. Late-phase studies were defined as phase III for CTUs, BioPharma and their sub-contractors (i.e., CROs), and phase IV for other participants (e.g. medical device companies).

A multi-stage approach was used to develop the survey. First, we identified the main criteria expected to impact site selection. Second, we organized these in four broad categories: (i) investigator-related, (ii) hospital/Institution-related, (iii) country/environment-related, and (iv) costs (evaluated both separately and within the environment category). Third, the defined criteria underwent review and discussion with a small number of knowledgeable professionals to ensure that potentially relevant criteria had not been missed (Figure 1).

The study group then built an internet-based survey hosted on a freely-

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accessible online questionnaire software (Survey Monkey, Palo Alto, CA, USA). Before launching the survey, healthcare market research experts (The Planning Shop International, London, UK) reviewed the survey design to optimize content and minimize bias. Additionally, a pilot survey undertaken by 15 respondents in June 2011 was used to validate and refine question content and organisation.

### Survey Procedure

The survey consisted of 23 questions, which took some 20 minutes to complete. In sequence, questions asked participants to (1) provide demographic information anonymously (2) rate the importance of each of the hypothesized trial site selection criteria for Europe as a whole, (3) provide perception of the trial environment in 12 European countries, and (4) rank areas of potential improvement. Participants' feedback was assessed using a multiple-choice format, requiring respondents to provide a single response of rank. The full set of questions is accessible at [http://www.sbg-marcom.ch/sat-eu/Study\\_plan.html](http://www.sbg-marcom.ch/sat-eu/Study_plan.html) The order of presentation of individual responses to each question was scrambled across respondents to minimise response bias. At the end of each section, a response box allowed participants to provide open text comments. ~~;~~ this additional material is available as an "on-line supplement". ~~while final~~ Results of the survey were thoroughly reviewed among the study group, and subsequently discussed with a 25-member expert panel in Brussels on November 2012. ~~The full set of questions is accessible at [http://www.sbg-marcom.ch/sat-eu/Study\\_plan.html](http://www.sbg-marcom.ch/sat-eu/Study_plan.html)~~

The survey was advertised through Industry and Clinical Trial Associations, online communities, social networks, and personal contacts of the SAT-EU Study group<sup>17</sup>. ~~so that the exact~~ precise number of people invited to participate is not known. No remuneration was provided to participants, but respondents were offered a summary of survey results once available.

Statistical Analysis

Given the descriptive nature of the SAT-EU study design, we did not formally estimate a required sample size. Instead, we sought to obtain at least 150 completed questionnaires from across the four stakeholder groups. Results are primarily presented descriptively as means (and 95% confidence intervals (95% CI)), or medians (and upper and lower quartiles), as appropriate to show results by group or country. Where data were available, responses were compared across three survey respondent groupings (i.e. CTU vs. CRO vs. industry), and across responses within each survey question, using one-way analysis of variance.

Results

A total of 485 individual responses were obtained, with participants providing responses to 72% of questions on average. Responders represented over 100 different institutions, including over 50 pharmaceutical, biotechnology or medical device firms, and over 20 CROs and CTUs.

Respondent Demographics

Respondents represented over 37 countries, the top five contributors being Italy, USA, UK, Germany, and Spain (Table 1). Participants were almost evenly split between BioPharma (49%) and CROs/CTUs (40%) (Figure 2). In terms of hierarchy/job description, 43% were vice-president, director, or manager in a research or marketing position, and an additional 20% were head of a CTU (Figure 3, Left Panel). The majority of respondents described themselves as being directly involved in trial site selection decisions; almost two-thirds either personally headed, or sat on the trial site selection committee of their organization (Figure 3, Right Panel). Importantly, most respondents were the final decision makers, stating that they were either the “overall final decision maker”, or that trial site selection decisions were “entirely at (their)

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discretion”.

**Table 1: Respondent work location (N=485)**

Country	Respondents
Australia	4
Austria	4
Belgium	21
Brazil	4
Bulgaria	3
Canada	6
China	4
Croatia	4
Czech Republic	4
Denmark	21
Egypt	4
Estonia	4
Finland	11
France	21
Germany	46
Greece	4
Hungary	4
India	13
Ireland	8
Israel	5
Italy	75
Netherlands	16
Nigeria	4
Norway	4
Poland	7
Portugal	9
Romania	7
Russia	4
Serbia	4
Slovakia	4
Slovenia	2
Spain	44
Sweden	13
Switzerland	20
Ukraine	4
United Kingdom	48
USA	58

Not Available 6

Relevance of investigator, environment, hospital, and costs criteria

Respondents were asked to divide 100 points (reflecting their perceived level of importance) across four categories of factors impacting trial site selection. For both early- and late-phase trials (as defined in Methods), factors pertaining to the investigator, the hospital/unit, and the environment, were rated at a high level of importance (25 or above) (Figure 4 Table 2). When combined, investigator- and hospital-dependent levers were reported to be instrumental in trial site choice for both early- and late-phase studies (average weight 60/100 and 57/100 respectively). In contrast, cost factors were considered to be less important for both early- and late-trials (P<0.0001) (Table 2 Figure 4). This pattern of response was consistent across survey respondent groupings (i.e. CTU vs. CRO vs. industry; not shown).

Investigator-Driven Criteria

Respondents were asked to assign 100 points across five investigator-related criteria. There was a statistically significant difference in the level of importance of the factors tested, with investigator track record in prior trials, experience in similar studies, and interest in study scoring a level of importance of 20 or above, while concurrent trial workload, and publication track record were significantly less important (P<0.0001) (Figure 5 Table 3). The pattern of response was again consistent across survey respondent groupings (not shown).

Environment-Driven Criteria

To explore environmental dynamics, respondents were asked to assign 100 points across six environment-related criteria. Market size/pool of eligible patients in the region, speed of approvals, and presence of disease management networks, were

assigned a greater level of importance. In contrast, costs of running trials, and particularly government financial/tax incentives were considered to be of significantly lower importance ( $P < 0.0001$ ) (Figure 6 Table 4). Also in this case, the pattern of response was consistent across survey respondent groupings (not shown).

#### *Investigator-Driven Criteria*

~~Respondents were asked to assign 100 points across five investigator related criteria. There was a statistically significant difference in the level of importance of the factors tested, with investigator track record in prior trials, experience in similar studies, and interest in study scoring a level of importance of 20 or above, while concurrent trial workload, and publication track record were significantly less important ( $P < 0.0001$ ) (Figure 6). The pattern of response was again consistent across survey respondent groupings (not shown).~~

#### *Hospital-Driven Criteria*

In this domain, 100 points had to be assigned across six criteria that explored characteristics of the specific hospital/unit where a clinical trial may potentially be run. There was a statistically significant difference in the level of importance of hospital-driven criteria, whereby site personnel experience and training, respondent's previous experience with site, and availability of facilities and equipment required by trial scored above 20 ( $P < 0.0001$ ). In contrast, site personnel language capabilities and hospital quality assurance process were significantly less important (Figure 7 Table 5).

#### *Perception of European Trial Environment*

Our survey showed a statistically significant difference in respondents' perceived desirability of running clinical trials across the twelve EU countries tested,

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i.e., Europe’s top 5 healthcare markets (Germany, France, Italy, the UK, and Spain), large east European markets (Poland, Hungary, Czech Republic), plus Netherlands, Belgium, Switzerland, and Austria. For both accessibility and transparency of all information required to run clinical trials (Figure 4.8 Upper Panel), and availability of equipment (not shown), Germany, UK and the Netherlands were the top three scorers. With regard to predictability and speed of Ethics Committees, Belgium was the top scorer, followed by Germany and the Netherlands (Figure 4.8 Lower Panel). In terms of overall trial site “desirability”, respondents scored Germany as the most desirable trial location, followed by the Netherlands and UK (P=0.0001) (Figure 59).

Possible Improvements

Two questions tested the hypothesis that making a site more visible would be desirable from the decision-makers’ perspective. We found that 83% of respondents would have been “much more likely” to include a site if all relevant investigator- and hospital-related information were readily available (Figure 6.40 Left Panel). Furthermore, 75% believed that web-site information would be either “definitely welcome”, or “useful most of the time” (Figure 6.40 Right Panel).

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## Discussion

The SAT-EU Study<sup>TM</sup> was a web-based survey designed to identify perceived drivers and hurdles associated with conducting clinical trials in Europe. We obtained responses from over four hundred participants in key stakeholder groups, i.e. BioPharma industry, medical device manufacturers, CROs, and CTUs. The vast majority of countries actively involved in clinical trials were represented, while most respondents were key decision makers in their organizations. These features allowed us to get direct and potentially relevant insights into the reasoning behind site selection for clinical trials.

Recent years have seen much public policy discussion on the need to foster Europe's role in medical research, and to rekindle its dwindling attractiveness for investment in clinical trials.<sup>18-20</sup> Various strategies have been proposed based on a "common sense" approach. Whilst possibly sound, policy recommendations were typically not founded on a systematic understanding of factors impacting clinical trial site selection. Indeed, one could argue that, borrowing from the rigour of its own discipline, medical policy decisions at all levels ought to be "evidence-based". Regrettably however, this approach seems to be largely absent. To our knowledge, the SAT-EU study is the first effort aimed at systematically investigating factors impacting trial site attractiveness across Europe. Given the survey's size, the variety of domains explored, the number of countries and organizations involved, and the prevalence of senior decision makers, our results may provide insight into "real world" trial site decisions.

Our study has several key findings. First, there was evidence of considerable variability in the perceived receptivity of European countries to undertake clinical trials, Germany, United Kingdom, and the Netherlands being rated the best markets. Reasons for greater appeal of certain countries are multiple. Larger countries could be

more attractive because of greater patient recruitment potential, and in prospect, because of the size of their markets. However, country size does not entirely explain the phenomenon, given the excellent results of small countries such as the Netherlands, and the low score of large countries such as Italy or Spain. Our survey sheds some light on this by pointing to the negative impact of administrative burden on clinical trial competitiveness. This is not only a concern at country level. Central to this discussion is the notion that the time required to collect information to determine a site's feasibility for inclusion in a trial, and to get it started, is also critical. Hence, the high weight placed on a site's proven track record in efficiently delivering results, which bears a relationship to specialized clinical research centres, and equally important, to the ability of clinical trial sponsors and organizers to access all of the required information quickly and effectively. Accordingly, the downsides of operating within a sub-optimal regulatory environment may not prejudice selection of an otherwise visible and competent investigator, whose trial site information is readily available and who is able to recruit the required patients. A third important finding of our survey is that contrary to a widely held tenet, costs of running trials - often invoked to explain why industry is going outside Europe<sup>6,16</sup> - as well as government incentives/tax breaks, are not the main considerations when selecting European sites. In other words, it would seem from stakeholders' feedback and follow-up discussions that to the extent that European centers may be excluded from a trial, the likely culprit is the hidden costs associated with excessive administrative time required to get a trial site up and running, not the high fees per enrolled patient. Although apparently surprising, the limited impact of costs needs to be considered against the backdrop of the various issues to which our survey tried to provide a response. Indeed, in addition to "direct" costs, a major negative factor is represented by indirect, or "hidden" costs, such as those characterized by time lost through layers of bureaucracy, slow recruitment by sites, or poor overall site performance. Hence, the importance of not only bureaucracy,

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but also of the level of training and trial expertise at sites. Additionally, the notion that investments in clinical trials in Europe cannot be easily improved through government incentives or tax breaks may have important implications in terms of public policy.

Comments obtained through Our survey ~~seem to clearly~~ indicates that stakeholders would like a single European “trial market” allowing them to gear trial site selection to expert investigators and to optimal patient recruitment, unobstructed by heterogeneous regulations or hurdles to obtaining crucial information. Participants expressed this need in two main ways. First, from a regulatory or “macro” perspective, they expressed desire for easier approval processes with less national variability and stronger pan-European element. This may indicate ethical committee approval timeframes, as well as institutional approvals at site level. Second, from a clinical research or “micro” perspective, respondents want access to transnational networks of disease-area experts, through visibility of experienced trial units via the internet and/or via participation in disease networks.

More than 50 years ago, the founders of the European Union envisioned a single market at the core of the European project. Despite this, a “single market” vision for clinical research did not develop as envisaged. This is damaging to an industry in which much of the investment in clinical trials is by necessity multinational. Indeed, Europe’s 2020 growth strategy calls for 3% of its Gross National Product to be invested in research and development (R&D) by 2020<sup>21</sup>. If this goal is to be achieved, BioPharma - the European sector with the highest R&D/Sales ratio<sup>22</sup> - should be allowed to invest in Europe without facing unnecessary roadblocks. Given the size of its healthcare market, its aging population, its well-established pharmaceutical industry, and the quality of its research centres and investigators, Europe has a formidable comparative advantage in clinical research. Individual European member states are well poised to take advantage of this by making the EU more competitive in clinical research. They should be encouraged to do so, not simply by investing in incentives or

tax breaks, but by implementing revisions to the CTD that are under consideration by member states, and by legislating removal of unhelpful bureaucratic barriers at national level. Improving hospital contracting, such as via national or even pan-European contract templates, would also significantly reduce administrative burden, speed up trial start, and make the European landscape significantly more competitive. On their part, the research community and relevant national bodies have a parallel imperative to ensure that hospitals and institutions are organised and networked more effectively, and that there is adequate training of trial staff. They need to ensure that clinical centres wishing to undertake more research are made more visible to industry and to international research communities, through dedicated research portals on their web sites, or by creating and/or joining disease networks. Finally, given that selected countries are consistently scored above others, a best practice audit of administrative provisions governing and supporting clinical trials in countries such as Germany, the UK, the Netherlands<sup>14</sup> would be helpful for drawing policy implications for other countries. The case for action rests on the realization that evidence-based policy is indeed possible in this arena. Learning from what is working successfully will facilitate the road to creating a more welcoming environment for clinical research in Europe.

**Limitations**

Consistent with voluntary surveys, we could only analyse responses provided by those who were interested in replying, and therefore we cannot exclude that other points of view may have emerged from those who did not participate.

~~However~~Nonetheless, it is rather reassuring that the responses were gathered through a fairly large number and range of people-professionals who belonged to a variety of organizations from a number of countries, and who were for the most part were the final decision makers in the process. However, - given that participation was largely through professional bodies and web-based communities, we are unable to

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~~provide an estimate of our coverage. have taken the time to respond to this survey, and the follow-up discussions held in an expert panel setting are~~ encouraging, as is ~~the finding that most of them were the final decision makers in the process, and that they belonged to a variety of organizations from a number of countries.~~ Whilst we took care in designing a survey that focused on the key determinants of trial site selection, we may have missed potentially important issues. We tried to minimize this through preliminary survey review and refinement with the help of external experts. ~~In addition, Finally,~~ some of our questions in relation to process and speed of approval may need further research to determine the root issues, as problems differ from country to country, and have to be weighed against the need to ensure that patient safety remains unprejudiced.

## Conclusions

Our study ~~indicates~~ ~~shows~~ that fostering European clinical research and attracting more trials to Europe does not require additional government spending. Instead, ~~we believe our findings support a more~~ ~~it requires~~ harmonised national adoption of ~~the clinical trial approvals process, revisions to the CTD,~~ greater visibility of transnational networks of disease experts, and greater accessibility to research system at national and pan-European levels. ~~Potential models for improvement include~~ ~~Carefully-crafted~~ harmonization of ~~ethical and institutional~~ approvals ~~systems~~, including aligned hospital contracting and greater visibility of centres of excellence, ~~which~~ may bring significantly more clinical research to Europe. Europe needs growth, and clinical research can play its part in directly stimulating economic activity while simultaneously boosting European innovation.

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European Biotech Industry Association (EuropaBio)

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European Vision Institute Clinical Research Network (Disease Network)

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EUCOMED Clinical Trial Interest Group

<http://www.eucomed.be/>

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### Competing Interests

All co-authors work in the area of healthcare, either academia or consulting, and as such have all been, or are involved in, the initiation, execution or interpretation of clinical trials. Accordingly, all co-authors have an intellectual/academic interest in seeing the European Clinical trial industry enhance its competitiveness. None of the authors however, stands to gain any more than any other member of the European healthcare community from the implementation of any of the recommendations made in the manuscript. We declare no other conflict of interest, and no other relationships or activities that could appear to have influenced the submitted work.

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### **Table 1: Respondent work location**

### **Table 2: Levers impacting trial site selection for early and late trials**

Respondents were asked to divide 100 points across the below 4 levers impacting their trial site selection for early phase studies:

(Pharma, Biotech, CROs, CTUs, answer for phase II studies)

(Medical device and all others answer for phase III studies)

and then for later phase studies:

(Pharma, Biotech, CROs, CTUs, answer for phase III studies)

(Medical device and all others answer for phase IV studies)

Bars represent mean and 95% Confidence Interval (N=341)

There was evidence of a statistically significant difference in the level of importance among the 4 factors ( $P < 0.0001$ )

### **Table 3: Investigator-driven criteria in selection of trial sites of phase II–III study sites (phase III–IV for medical devices)**

Respondents were asked to rate investigator-driven criteria by dividing 100 points across 5 criteria potentially relevant in selecting trial sites for phase III studies:

(Pharma, Biotech, CROs, CTUs, answer for phase III studies)

(Medical device and all others answer for phase IV)

Bars represent mean and 95% Confidence Interval (N=341)

There was evidence of a statistically significant difference in the level of importance among the 5 criteria ( $P < 0.0001$ )

### **Table 4: Environment-driven criteria in selection of trial sites of phase II–III study sites (phase III–IV for medical devices)**

Respondents were asked to rate environment-driven criteria by dividing 100 points across 6 criteria potentially relevant in selecting trial sites for phase III studies:

(Pharma, Biotech, CROs, CTUs, answer for phase III studies)

(Medical device and all others answer for phase IV)

Bars represent mean and 95% Confidence Interval (N=341)

There was evidence of a statistically significant difference in the level of importance among the 6 criteria ( $P < 0.0001$ )

### **Table 5: Hospital-driven criteria in selection of phase II–III study sites (phase III–IV for medical devices)**

Respondents were asked to rate Hospital driven criteria by dividing 100 points across 6 criteria potentially relevant in selecting trial sites for phase III studies:

(Pharma, Biotech, CROs, CTUs, answer for phase III studies)

(Medical device and all others answer for phase IV)

Bars represent mean and 95% Confidence Interval (N=342)

There was evidence of a statistically significant difference in the level of importance among the 6 criteria (P < 0.0001)

**Figure 1: Hypothesis about trial site selection criteria**

Four categories of levers potentially impacting trial site selection were identified. Survey weighed relevance across these four levers, then drilled down for weight within each sub-category.

**Figure 2: Respondent's Organization**

Respondents were asked to answer the question: "Please indicate which organisation most closely resembles yours"  
Bars show percent distribution of 485 individual responses

**Abbreviations**

- Pharma = Industry: Pharmaceutical Company
- CRO = Clinical Research Organisation
- CTU = Academic Clinical Trial Unit
- Biotech = Industry: Biotechnology Company

Medical Devices included: Medical Devices, Radiological, Electro-medical or HealthCare Information Technology

"Other" included following self-reported categories:

- Respondent working for a mixed portfolio industry with either Pharma/Biotech portfolio or Pharm/Medical Device portfolio (self reported)
- Regulatory/Clinical Consultant
- Hospital or private clinic

**Figure 3**

**Left Panel: Respondent hierarchy**

Respondents were asked to answer the question: "Please indicate the position which most closely resembles yours"

Chart shows percent distribution of 485 individual responses

VP = Vice President

~~CTU = Clinical Trial Unit~~

~~CRO = Clinical Research Organisation~~

"Others" were respondents who wanted to be more specific in their titles:

- Global Study Manager/Clinical Research Associate
- Regulatory Affairs/ Regulatory in a Clinical department/ Good Clinical Practice Quality Assurance Manager, or Director/ Safety Pharmacovigilance Officer
- Medical Affairs/ Medical Director/Clinical Director/Global Scientific Affairs
- General Manager
- "Professor or Lecturer"

**Right Panel: Respondent organisation's decision-making process**

Respondents were asked to answer the question: "Please indicate which most closely resembles how trial site selection decisions are made at your institution"

Chart shows percent distribution of 485 individual responses

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Other included:

- My staff decides
- Decision outsourced to CRO
- CRA decides
- Decisions according to Standard Operation Procedures
- Many people involved in decision, or Study Team decides
- Our affiliates decide

#### **Figure 24: Levers impacting trial site selection for early and late trials**

Respondents were asked to divide 100 points across the below 4 levers impacting their trial site selection for early phase studies:

(Pharma, Biotech, CROs, CTUs, answer for phase II studies)

(Medical device and all others answer for phase III studies)

and then for later phase studies:

(Pharma, Biotech, CROs, CTUs, answer for phase III studies)

(Medical device and all others answer for phase IV studies)

Bars represent mean and 95% Confidence Interval (N=341)

There was evidence of a statistically significant difference in the level of importance among the 4 factors ( $P < 0.0001$ )

#### **Figure 5: Environment driven criteria in selection of trial sites of phase II–III study sites (phase III–IV for medical devices)**

Respondents were asked to rate environment driven criteria by dividing 100 points across 6 criteria potentially relevant in selecting trial sites for phase III studies:

(Pharma, Biotech, CROs, CTUs, answer for phase III studies)

(Medical device and all others answer for phase IV)

Bars represent mean and 95% Confidence Interval (N=341)

There was evidence of a statistically significant difference in the level of importance among the 6 criteria ( $P < 0.0001$ )

#### **Figure 6: Investigator driven criteria in selection of trial sites of phase II–III study sites (phase III–IV for medical devices)**

Respondents were asked to rate investigator driven criteria by dividing 100 points across 5 criteria potentially relevant in selecting trial sites for phase III studies:

(Pharma, Biotech, CROs, CTUs, answer for phase III studies)

(Medical device and all others answer for phase IV)

Bars represent mean and 95% Confidence Interval (N=341)

There was evidence of a statistically significant difference in the level of importance among the 5 criteria ( $P < 0.0001$ )

#### **Figure 75: Hospital driven criteria in selection of phase II–III study sites (phase III–IV for medical devices)**

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~~Respondents were asked to rate Hospital driven criteria by dividing 100 points across 6 criteria potentially relevant in selecting trial sites for phase III studies: (Pharma, Biotech, CROs, CTUs, answer for phase III studies) (Medical device and all others answer for phase IV). Bars represent mean and 95% Confidence Interval (N=342). There was evidence of a statistically significant difference in the level of importance among the 6 criteria (P < 0.0001).~~

**Figure 48**  
**Upper Panel**  
**Accessibility and transparency of all types of information required to make trial site selection decisions - Twelve country rank (N=296)**

Respondents were asked to rate twelve countries for the accessibility and transparency of information (of all types) required to make trial site selection  
Bars represent mean and 95% Confidence Interval (N=296)

Statistically significant difference in satisfaction across EU countries (P = 0.0001)

**Lower Panel**  
**Predictability and speed of Ethics Committees and IRBs for phase II–III multi-centre RCTs - Twelve country rank (N=296)**

Respondents were asked to rate twelve countries for the speed of their ethics committees & IRBs for phase III (3) multi centric RCTs  
Bars represent mean and 95% Confidence Interval (number of respondents in parentheses)

Statistically significant difference in satisfaction across EU countries (P = 0.0001)  
IRB = institutional review board

**Figure 95: Trial Site Desirability by country**  
**Trial Site Desirability “Index” - Nine Country Rank**

Respondents were asked to provide their "personal perception" ranking of the desirability of running trials in 9 countries, ranking them from (1) "most desirable" country to (9) "least desirable" country (if needed, they could click "no opinion" in up to three countries they know the least)  
Data are presented as whisker-box plot of median and lower and upper quartile

There was evidence of a statistically significant difference in the perceived desirability of running trials across EU countries (P = 0.0001)

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**Figure 640**

**Left Panel: Likelihood of selecting trial site given relevant information**

Respondents were asked to rate their level of agreement with the statement:  
"I am much more likely to select a trial site if I have all of the relevant Investigator and Site specific information easily available to me"  
Chart represents percent response (N=253)

**Right Panel: Usefulness of trial site web site information**

Respondents were asked to pick the statement that they felt closest to with reference to the assertion that "it would be useful to have relevant trial information readily visible in a dedicated public section the Hospital's web site (Facilities, equipment, personnel qualification, Ethics Committee and Institutional Review Board timings, contact people for trials, etc.)"

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**Factors Influencing Clinical Trial Site Selection in Europe:  
The Survey of Attitudes towards Trial sites in Europe  
(The SAT-EU Study™)**

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**Factors Influencing Clinical Trial Site Selection in Europe:  
The Survey of Attitudes towards Trial sites in Europe  
(The SAT-EU Study™)**

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## European Trial Site Selection Criteria - The SAT-EU Study™

### Abstract (300 words)

**Objectives:** Applications to run clinical trials in Europe fell 25% between 2007 and 2011. Costs, speed of approvals, and shortcomings of European Clinical Trial Directive are commonly invoked to explain this unsatisfactory performance. However, no hard evidence is available on the actual weight of these factors, nor has it been previously investigated whether other criteria may also impact clinical trial site selection.

**Design:** The SAT-EU Study™ was an anonymous, cross-sectional Web-based survey that systematically assessed factors impacting European clinical trial site selection. It explored 19 factors across investigator-, hospital-, and environment-driven criteria, and costs. It also surveyed perceptions of the European trial environment.

**Setting and Participants:** Clinical Research Organizations (CROs), academic Clinical Trial Units (CTUs), and Industry invited to respond.

**Interventions:** None

**Outcome measures:** Primary: Weight assigned to each factor hypothesized to impact trial site selection and trial incidence; Secondary: Desirability of European countries to run clinical trials

**Results:** Responses were obtained from 485 professionals in 34 countries: 49% from BioPharma, 40% from CTUs or CROs. Investigator-, environment-, and hospital-dependent factors were rated highly important, costs being less important ( $P<0.0001$ ). Within environment-driven criteria, pool of eligible patients, speed of approvals, and presence of disease-management networks were significantly more important than costs or government financial incentives ( $P<0.0001$ ). The pattern of response was consistent across respondent groupings (CTU vs. CRO vs. Industry). Considerable variability was demonstrated in the perceived receptivity of countries to undertake clinical trials, with Germany, United Kingdom, and the Netherlands rated the best trial markets ( $P<0.0001$ ).

**Conclusions:** Investigator-dependent factors and ease of approval dominate trial site selection, while costs appear less important. Fostering competitiveness of European clinical research may not require additional government spending/incentives. Rather, harmonization of approval processes, greater visibility of centres of excellence, and reduction of “hidden” indirect costs, may bring significantly more clinical trials to Europe.

**Article summary (292 words)**

**Article focus**

- Applications to perform clinical trials in the EU fell 25% from 2007 to 2011, with bureaucracy, the EU clinical trial directive 2001/20/EC, and costs reportedly to blame. Yet, the clinical research community lacks a systematic assessment of the relative weight of these and other criteria that may impact the viability of conducting clinical trials in Europe.
- The SAT-EU Study compiled the input of 485 decision makers to: (a) systematically evaluate 19 factors possibly impacting site selection for multicentre trials for which Europe is under consideration, and (b) to assess the relative desirability of doing trials in 12 European countries. The web-based survey was blinded and response choices were scrambled

**Key Messages**

- Costs, and even more so government incentives, carry a surprisingly low weight, while investigator- and environment-dependent factors dominate trial site selection decisions
- Not previously highlighted is the fact that the viability of conducting trials in Europe is also a function of the availability of critical information to get centres recruited and trials started, such as via participation in Disease Area Networks and web research portals
- Germany, UK, and the Netherlands are seen as the best trial markets

**Strengths and Limitations**

- *Strength:* We provide systematic evidence across a large sample of expert professionals indicating that fostering competitiveness of European clinical research may not require additional government spending/incentives. Carefully crafted harmonization of approvals, greater visibility of centres of excellence via disease networks/the web, and reduction of “hidden” costs are more likely to boost competitiveness of European clinical research
- *Limitations:* Consistent with voluntary surveys, we could only analyse responses provided by those interested in replying, and therefore cannot exclude that other points of view may have emerged from those who did not participate; our questionnaire may also have missed potentially important factors

## Introduction

Europe has consistently expressed a desire to maintain and improve clinical trial competitiveness,<sup>1-3</sup> most recently by advocating a “European Research Area” in which “researchers, scientific knowledge and technology circulate freely.”<sup>4</sup> A major component of the European governance for clinical research, European Clinical Trial Directive 2001/20/EC (CTD) was intended to support this goal, focussing on the harmonisation of research processes across EU member states.<sup>5-9</sup> However, the CTD failed to achieve its intended impact on the simplification and harmonization of administrative provisions governing clinical trials<sup>9</sup>, and thus on the level of European clinical research activity.<sup>2,10-11</sup> In fact, from 2007 to 2011, the number of clinical trial applications in Europe fell 25%<sup>12</sup>. Accordingly, although concerted calls for further CTD revisions continue<sup>13-14</sup> and recommendations awaiting member state review have been made by European Commission<sup>6</sup> and endorsed by scientific societies,<sup>15</sup> it is not clear which specific recommendations should be implemented or prioritized at either national or pan-European level.

Much of this uncertainty stems from insufficient understanding of the key drivers determining decision made by the healthcare industry, academic clinical trial units (CTUs), and clinical research organizations (CROs) in selecting European trial sites. Furthermore, although it is widely believed that costs and speed of approval are key factors influencing clinical trial incidence in Europe,<sup>6,16</sup> the relative weight of these and other important criteria is poorly understood. To our knowledge, no published studies have examined country and site selection criteria for trials conducted in Europe. Evidence is therefore needed to improve our understanding of stakeholders’ decision-making process.

The Survey of Attitudes towards Trial sites in Europe (The SAT-EU Study™) was established as a non-profit collaborative effort to systematically assess factors

impacting clinical trial site selection in Europe. We also investigated whether trial selection needs differ between academic and commercial sponsors. Finally, the survey sought to explore perceptions of the current European trial environment, and to identify areas for future improvement.

**Methods**

*Survey design*

The SAT-EU Study was an anonymous web-based cross-sectional survey undertaken between September 26<sup>th</sup> 2011, and January 21<sup>st</sup>, 2012. It included all stakeholder groups involved in clinical trial site selection, i.e., BioPharma companies, Medical Device manufacturers, CROs, and CTUs. The survey sought to capture information on both early- and late-phase studies. Late-phase studies were defined as phase III for CTUs, BioPharma and their sub-contractors (i.e., CROs), and phase IV for other participants (e.g. medical device companies).

A multi-stage approach was used to develop the survey. First, we identified the main criteria expected to impact site selection. Second, we organized these in four broad categories: (i) investigator-related, (ii) hospital/Institution-related, (iii) country/environment-related, and (iv) costs (evaluated both separately and within the environment category). Third, the defined criteria underwent review and discussion with a small number of knowledgeable professionals to ensure that potentially relevant criteria had not been missed (Figure 1).

The study group then built an internet-based survey hosted on a freely-accessible online questionnaire software (Survey Monkey, Palo Alto, CA, USA). Before launching the survey, healthcare market research experts (The Planning Shop International, London, UK) reviewed the survey design to optimize content and minimize bias. Additionally, a pilot survey undertaken by 15 respondents in June 2011

was used to validate and refine question content and organisation.

### *Survey Procedure*

The survey consisted of 23 questions, which took some 20 minutes to complete. In sequence, questions asked participants to (1) provide demographic information anonymously (2) rate the importance of each of the hypothesized trial site selection criteria for Europe as a whole, (3) provide perception of the trial environment in 12 European countries, and (4) rank areas of potential improvement. Participants' feedback was assessed using a multiple-choice format, requiring respondents to provide a single response of rank. The full set of questions is accessible at [http://www.sbg-marcom.ch/sat-eu/Study\\_plan.html](http://www.sbg-marcom.ch/sat-eu/Study_plan.html). The order of presentation of individual responses to each question was scrambled across respondents to minimise response bias. At the end of each section, a response box allowed participants to provide open text comments, available as an "online supplement". Results of the survey were thoroughly reviewed among the study group, and subsequently discussed with a 25-member expert panel in Brussels on November 2012.

The survey was advertised through Industry and Clinical Trial Associations, online communities, social networks, and personal contacts of the SAT-EU Study group<sup>17</sup>, so that the precise number of people invited to participate is not known. No remuneration was provided to participants, but respondents were offered a summary of survey results once available.

### *Statistical Analysis*

Given the descriptive nature of the SAT-EU study design, we did not formally estimate a required sample size. Instead, we sought to obtain at least 150 completed questionnaires from across the four stakeholder groups. Results are primarily

presented descriptively as means (and 95% confidence intervals (95% CI)), or medians (and upper and lower quartiles), as appropriate to show results by group or country. Where data were available, responses were compared across three survey respondent groupings (i.e. CTU vs. CRO vs. industry), and across responses within each survey question, using one-way analysis of variance.

**Results**

A total of 485 individual responses were obtained, with participants providing responses to 72% of questions on average. Responders represented over 100 different institutions, including over 50 pharmaceutical, biotechnology or medical device firms, and over 20 CROs and CTUs.

*Respondent Demographics*

Respondents represented over 37 countries, the top five contributors being Italy, USA, UK, Germany, and Spain (Table 1). Participants were almost evenly split between BioPharma (49%) and CROs/CTUs (40%) (Figure 2). In terms of hierarchy/job description, 43% were vice-president, director, or manager in a research or marketing position, and an additional 20% were head of a CTU (Figure 3, Left Panel). The majority of respondents described themselves as being directly involved in trial site selection decisions; almost two-thirds either personally headed, or sat on the trial site selection committee of their organization (Figure 3, Right Panel). Importantly, most respondents were the final decision makers, stating that they were either the “overall final decision maker”, or that trial site selection decisions were “entirely at (their) discretion”.

*Relevance of investigator, environment, hospital, and costs criteria*

Respondents were asked to divide 100 points (reflecting their perceived level of

importance) across four categories of factors impacting trial site selection. For both early- and late-phase trials (as defined in Methods), factors pertaining to the investigator, the hospital/unit, and the environment, were rated at a high level of importance (25 or above) (Table 2). When combined, investigator- and hospital-dependent levers were reported to be instrumental in trial site choice for both early- and late-phase studies (average weight 60/100 and 57/100 respectively). In contrast, cost factors were considered to be less important for both early- and late-trials ( $P<0.0001$ ) (Table 2). This pattern of response was consistent across survey respondent groupings (i.e. CTU vs. CRO vs. industry; not shown).

#### *Investigator-Driven Criteria*

Respondents were asked to assign 100 points across five investigator-related criteria. There was a statistically significant difference in the level of importance of the factors tested, with investigator track record in prior trials, experience in similar studies, and interest in study scoring a level of importance of 20 or above, while concurrent trial workload, and publication track record were significantly less important ( $P<0.0001$ ) (Table 3). The pattern of response was again consistent across survey respondent groupings (not shown).

#### *Environment-Driven Criteria*

To explore environmental dynamics, respondents were asked to assign 100 points across six environment-related criteria. Market size/pool of eligible patients in the region, speed of approvals, and presence of disease management networks, were assigned a greater level of importance. In contrast, costs of running trials, and particularly government financial/tax incentives were considered to be of significantly lower importance ( $P<0.0001$ ) (Table 4). Also in this case, the pattern of response was consistent across survey respondent groupings (not shown).

#### *Hospital-Driven Criteria*

In this domain, 100 points had to be assigned across six criteria that explored

characteristics of the specific hospital/unit where a clinical trial may potentially be run. There was a statistically significant difference in the level of importance of hospital-driven criteria, whereby site personnel experience and training, respondent's previous experience with site, and availability of facilities and equipment required by trial scored above 20 ( $P<0.0001$ ). In contrast, site personnel language capabilities and hospital quality assurance process were significantly less important (Table 5).

*Perception of European Trial Environment*

Our survey showed a statistically significant difference in respondents' perceived desirability of running clinical trials across the twelve EU countries tested, i.e., Europe's top 5 healthcare markets (Germany, France, Italy, the UK, and Spain), large east European markets (Poland, Hungary, Czech Republic), plus Netherlands, Belgium, Switzerland, and Austria. For both accessibility and transparency of all information required to run clinical trials (Figure 4, Upper Panel), and availability of equipment (not shown), Germany, UK and the Netherlands were the top three scorers. With regard to predictability and speed of Ethics Committees, Belgium was the top scorer, followed by Germany and the Netherlands (Figure 4, Lower Panel). In terms of overall trial site "desirability", respondents scored Germany as the most desirable trial location, followed by the Netherlands and UK ( $P=0.0001$ ) (Figure 5).

*Possible Improvements*

Two questions tested the hypothesis that making a site more visible would be desirable from the decision-makers' perspective. We found that 83% of respondents would have been "much more likely" to include a site if all relevant investigator- and hospital-related information were readily available (Figure 6, Left Panel). Furthermore, 75% believed that web-site information would be either "definitely welcome", or "useful most of the time" (Figure 6, Right Panel).

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**Discussion**

The SAT-EU Study™ was a web-based survey designed to identify perceived drivers and hurdles associated with conducting clinical trials in Europe. We obtained responses from over four hundred participants in key stakeholder groups, i.e. BioPharma industry, medical device manufacturers, CROs, and CTUs. The vast majority of countries actively involved in clinical trials were represented, while most respondents were key decision makers in their organizations. These features allowed us to get direct and potentially relevant insights into the reasoning behind site selection for clinical trials.

Recent years have seen much public policy discussion on the need to foster Europe’s role in medical research, and to rekindle its dwindling attractiveness for investment in clinical trials.<sup>18-20</sup> Various strategies have been proposed based on a “common sense” approach. Whilst possibly sound, policy recommendations were typically not founded on a systematic understanding of factors impacting clinical trial site selection. Indeed, one could argue that, borrowing from the rigour of its own discipline, medical policy decisions at all levels ought to be “evidence-based”. Regretfully however, this approach seems to be largely absent. To our knowledge, the SAT-EU study is the first effort aimed at systematically investigating factors impacting trial site attractiveness across Europe. Given the survey’s size, the variety of domains explored, the number of countries and organizations involved, and the prevalence of senior decision makers, our results may provide insight into “real world” trial site decisions.

Our study has several key findings. First, there was evidence of considerable variability in the perceived receptivity of European countries to undertake clinical trials, Germany, United Kingdom, and the Netherlands being rated the best markets. Reasons for greater appeal of certain countries are multiple. Larger countries could be

more attractive because of greater patient recruitment potential, and in prospect, because of the size of their markets. However, country size does not entirely explain the phenomenon, given the excellent results of small countries such as the Netherlands, and the low score of large countries such as Italy or Spain. Our survey sheds some light on this by pointing to the negative impact of administrative burden on clinical trial competitiveness. This is not only a concern at country level. Central to this discussion is the notion that the time required to collect information to determine a site's feasibility for inclusion in a trial, and to get it started, is also critical. Hence, the high weight placed on a site's proven track record in efficiently delivering results, which bears a relationship to specialized clinical research centres, and equally important, to the ability of clinical trial sponsors and organizers to access all of the required information quickly and effectively. Accordingly, the downsides of operating within a sub-optimal regulatory environment may not prejudice selection of an otherwise visible and competent investigator, whose trial site information is readily available and who is able to recruit the required patients. A third important finding of our survey is that contrary to a widely held tenet, costs of running trials - often invoked to explain why industry is going outside Europe<sup>6,16</sup> - as well as government incentives/tax breaks, are not the main considerations when selecting European sites. In other words, it would seem from stakeholders' feedback and follow-up discussions that to the extent that European centers may be excluded from a trial, the likely culprit is the hidden costs associated with excessive administrative time required to get a trial site up and running, not the high fees per enrolled patient. Although apparently surprising, the limited impact of costs needs to be considered against the backdrop of the various issues to which our survey tried to provide a response. Indeed, in addition to "direct" costs, a major negative factor is represented by indirect, or "hidden" costs, such as those characterized by time lost through layers of bureaucracy, slow recruitment by sites, or poor overall site performance. Hence, the importance of not only bureaucracy, but also of the level of training and trial expertise at sites. Additionally, the notion that

investments in clinical trials in Europe cannot be easily improved through government incentives or tax breaks may have important implications in terms of public policy. Comments obtained through our survey seem to indicate that stakeholders would like a single European “trial market” allowing them to gear trial site selection to expert investigators and to optimal patient recruitment, unobstructed by heterogeneous regulations or hurdles to obtaining crucial information. Participants expressed this need in two main ways. First, from a regulatory or “macro” perspective, they expressed desire for easier approval processes with less national variability and stronger pan-European element. This may indicate ethical committee approval timeframes, as well as institutional approvals at site level. Second, from a clinical research or “micro” perspective, respondents want access to transnational networks of disease-area experts, through visibility of experienced trial units via the internet and/or via participation in disease networks.

More than 50 years ago, the founders of the European Union envisioned a single market at the core of the European project. Despite this, a “single market” vision for clinical research did not develop as envisaged. This is damaging to an industry in which much of the investment in clinical trials is by necessity multinational. Indeed, Europe’s 2020 growth strategy calls for 3% of its Gross National Product to be invested in research and development (R&D) by 2020<sup>21</sup>. If this goal is to be achieved, BioPharma - the European sector with the highest R&D/Sales ratio<sup>22</sup> - should be allowed to invest in Europe without facing unnecessary roadblocks. Given the size of its healthcare market, its aging population, its well-established pharmaceutical industry, and the quality of its research centres and investigators, Europe has a formidable comparative advantage in clinical research. Individual European member states are well poised to take advantage of this by making the EU more competitive in clinical research. They should be encouraged to do so, not simply by investing in incentives or tax breaks, but by implementing revisions to the CTD that are under consideration by member states, and by legislating removal of unhelpful bureaucratic barriers at national

level. Improving hospital contracting, such as via national or even pan-European contract templates, would also significantly reduce administrative burden, speed up trial start, and make the European landscape significantly more competitive. On their part, the research community and relevant national bodies have a parallel imperative to ensure that hospitals and institutions are organised and networked more effectively, and that there is adequate training of trial staff. They need to ensure that clinical centres wishing to undertake more research are made more visible to industry and to international research communities, through dedicated research portals on their web sites, or by creating and/or joining disease networks. Finally, given that selected countries are consistently scored above others, a best practice audit of administrative provisions governing and supporting clinical trials in countries such as Germany, the UK, the Netherlands<sup>14</sup> would be helpful for drawing policy implications for other countries. The case for action rests on the realization that evidence-based policy is indeed possible in this arena. Learning from what is working successfully will facilitate the road to creating a more welcoming environment for clinical research in Europe.

## Limitations

Consistent with voluntary surveys, we could only analyse responses provided by those who were interested in replying, and therefore we cannot exclude that other points of view may have emerged from those who did not participate. Nonetheless, it is rather reassuring that the responses were gathered through a fairly large number of professionals who belonged to a variety of organizations from a number of countries, and who were for the most part the final decision makers in the process. However, given that participation was largely through professional bodies and web-based communities, we are unable to provide an estimate of our coverage. Whilst we took care in designing a survey that focused on the key determinants of trial site selection, we may have missed potentially important issues. We tried to minimize this through preliminary survey review and refinement with the help of external experts. Also,

although we aimed at obtaining data relative to both industry-sponsored and not-for-profit clinical trials, it is possible that responses preferentially captured the former. In addition, some of our questions relating to process and speed of approval may need further research to determine the root issues, as problems differ from country to country, and have to be weighed against the need to ensure that patient safety remains unprejudiced.

**Conclusions**

Our study indicates that fostering European clinical research and attracting more trials to Europe does not require additional government spending. Instead, we believe our findings support a more harmonised national adoption of the clinical trial approvals process, greater visibility of transnational networks of disease experts, and greater accessibility to research system at national and pan-European levels. Potential models for improvement include harmonization of ethical and institutional approvals systems, including aligned hospital contracting and greater visibility of centres of excellence, which may bring significantly more clinical research to Europe. Europe needs growth, and clinical research can play its part in directly stimulating economic activity while simultaneously boosting European innovation.

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Applied Clinical Trials (ACT)

<http://www.appliedclinicaltrialsonline.com/>

European Forum for Good Clinical Practice (EFGCP)

<http://www.efgcp.be>

European Federation of Pharmaceutical Industry Associations (EFPIA)

<http://www.efpia.eu/>

European Biotech Industry Association (EuropaBio)

<http://www.europabio.org/>

Perugia University, Italy

<http://facolta.unipg.it/medicina/>

Drug Information Association (DIA)

<http://www.diahome.org/DIAHome/Home.aspx>

Virtuoso Consulting, Geneva, Switzerland

<http://www.virtuoso.ch/model.html>

European Vision Institute Clinical Research Network (Disease Network)

<http://www.evicr.net>

EUCOMED Clinical Trial Interest Group

<http://www.eucomed.be/>

Pharma IQ

<http://www.pharma-iq.com/>

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**Authors' contributions**

MG: survey design and implementation; critical data analysis; manuscript drafting; overall project supervision  
RT: survey design; statistical analysis; final manuscript editing  
MM: survey design and implementation; survey advertising and data collection; critical data analysis; final manuscript editing  
BC: survey design and implementation; survey advertising and data collection; critical data analysis; final manuscript editing  
AP: survey design and implementation; survey advertising and data collection; critical data analysis; final manuscript editing  
GG: survey design and implementation; critical data analysis; final manuscript editing  
GA: survey design and implementation; critical data analysis; manuscript drafting; overall project supervision

**Data Sharing**

Extra data is available in the form of raw survey data, providing individual (blinded) responses for each of 485 respondents. This data can be accessed either directly on the Survey Monkey platform or downloaded to excel from Survey Monkey. Our statistical analysis is also available upon request. Extra data is available by emailing [giuseppe.ambrosio@ospedale.perugia.it](mailto:giuseppe.ambrosio@ospedale.perugia.it)

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**Competing Interests**

All co-authors work in the area of healthcare, either academia or consulting, and as such have all been, or are involved in, the initiation, execution or interpretation of clinical trials. Accordingly, all co-authors have an intellectual/academic interest in seeing the European Clinical trial industry enhance its competitiveness. None of the authors however, stands to gain any more than any other member of the European healthcare community from the implementation of any of the recommendations made in the manuscript. We declare no other conflict of interest, and no other relationships or activities that could appear to have influenced the submitted work.

The study group has received acknowledgement permission from each of the institutions acknowledged for having helped to collect survey participants. Participation in the survey was voluntary and not associated with any remuneration.

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Table 1: Respondent work location (N=485)

Country	Respondents
Australia	1
Austria	4
Belgium	21
Brazil	1
Bulgaria	3
Canada	6
China	1
Croatia	1
Czech Republic	1
Denmark	21
Egypt	1
Estonia	1
Finland	11
France	21
Germany	46
Greece	4
Hungary	4
India	13
Ireland	8
Israel	5
Italy	75
Netherlands	16
Nigeria	1
Norway	1
Poland	7
Portugal	9
Romania	7
Russia	1
Serbia	1
Slovakia	1
Slovenia	2
Spain	44
Sweden	13
Switzerland	20
Ukraine	1
United Kingdom	48
USA	58
Not Available	6

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Table 2 Levers impacting trial site selection for early and late trials						
Lever	Response Mean		Upper 95% Confidence Limit (U95CL)		Lower 95% Confidence Limit (U95CL)	
	Early Phase	Late Phase	Early Phase	Late Phase	Early Phase	Late Phase
Investigator factors	30.2	29.1	31.5	30.4	28.9	27.8
Hospital/unit factors	28.4	28.3	29.7	29.7	27.0	26.9
Environmental factors	25.5	23.5	26.6	24.7	24.3	22.4
Cost factors	16.0	19.0	17.2	20.4	14.7	17.7

**Legend for Table 2**

Respondents (N=341) were asked to divide 100 points across the above 4 levers impacting their trial site selection for early phase studies:

- Pharma, Biotech, CROs, CTUs, answered for phase II (2) studies
- Medical device and all others answered for phase III (3) studies

Then respondents were asked to do the same as above for later phase studies:

- Pharma, Biotech, CROs, CTUs, answered for phase III (3) studies
- Medical device and all others answered for phase IV (4) studies

There was evidence of a statistically significant difference in the level of importance of the 4 factors (P < 0.0001)

The pattern of response (not shown here) appeared to be consistent across survey respondent groupings (i.e. CTU vs. CRO vs. industry)

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**Table 3**  
Investigator-driven criteria in selection of phase II-III trial sites  
(Phase III-IV for medical device)

Criteria	Mean	Upper 95% Confidence Limit (U95CL)	Lower 95% Confidence Limit (U95CL)	Standard Deviation
Investigator recruitment/retention track record	27.3	28.5	22.4	13.3
Investigator experience in previous trials	22.7	23.8	21.6	12.0
Investigator interest	22.42	23.6	21.3	13.4
Investigator concurrent workload	17.2	18.2	16.2	9.8
Investigator publication track record	10.4	11.3	9.6	10.9

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**Legend for Table 3:**  
Respondents (N=341) were asked to divide 100 points across the above 5 criteria when selecting trial sites for phase III/IV (3/4) studies:  
– Pharma, Biotech, CROs, CTUs answered for phase III (3) studies  
– Medical device and all others answered for phase IV (4) studies

There was evidence of a statistically significant difference in the level of importance of the 5 criteria (P < 0.0001)  
The pattern of response (not shown here) appeared to be consistent across survey respondent groupings  
(i.e. CTU vs. CRO vs. industry)

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**Table 4**

**Environment-driven criteria in selection of phase II-II trial sites  
(Phase III-IV for medical devices)**

Criteria	Average	Upper 95% Confidence Limit (U95CL)	Lower 95% Confidence Limit (U95CL)	Standard Deviation
<b>Size of market/eligible patients in region</b>	23.8	25.2	22.4	13.3
<b>Speed of MoH/Ethics Committees approval</b>	23.4	24.6	22.1	12.0
<b>Disease management system/networks</b>	18.9	20.4	17.5	13.4
<b>Cost of running trial</b>	15.2	16.3	14.2	9.8
<b>Presence of country on "core country list"</b>	11.8	13.0	10.7	10.9
<b>Government financial/tax incentives</b>	6.9	7.6	6.2	6.6

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**Legend for Table 4**

Respondents (N=341) were asked to divide 100 points across the above 6 criteria when selecting trial sites for phase III/ IV (3/4) studies:

- Pharma, Biotech, CROs, CTUs answered for phase III (3) studies
- Medical device and all others answered for phase IV (4) studies

There was evidence of a statistically significant difference in the level of importance of the 6 criteria (P < 0.0001)

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<b>Table 5</b> <b>Hospital-driven criteria in selection of phase II-III trial sites</b> <b>(Phase III-IV for medical devices)</b>			
	Average	Upper 95% Confidence Limit (U95CL)	Lower 95% Confidence Limit (U95CL)
Site personnel experience and training	22.0	23.1	20.84
Previous experience with site	20.0	21.2	18.7
Facilities/equipment required by trial	19.7	20.7	18.7
Hospital approval/contracting system	17.4	18.5	16.4
Site personnel language proficiency	10.8	11.7	10.0
Hospital Quality Assurance process	10.1	10.9	9.2

\*Sample Size=341

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**Legend for Table 5:**

Respondents (N=341) were asked to rate Hospital driven criteria by dividing 100 points across 6 criteria potentially used when selecting trial sites for phase III studies:  
-Pharma, Biotech, CROs, CTUs, answer for phase III studies  
-Medical device and all others answer for phase IV

There was evidence of a statistically significant difference in the level of importance of the 6 criteria (P < 0.0001)

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**Table and Figure Legend**

**Table 1: Respondent work location**

**Table 2: Levers impacting trial site selection for early and late trials**

Respondents were asked to divide 100 points across the below 4 levers impacting their trial site selection for early phase studies:  
(Pharma, Biotech, CROs, CTUs, answer for phase II studies)  
(Medical device and all others answer for phase III studies)

and then for later phase studies:  
(Pharma, Biotech, CROs, CTUs, answer for phase III studies)  
(Medical device and all others answer for phase IV studies)  
Bars represent mean and 95% Confidence Interval (N=341)

There was evidence of a statistically significant difference in the level of importance among the 4 factors ( $P < 0.0001$ )

**Table 3: Investigator-driven criteria in selection of trial sites of phase II–III study sites (phase III–IV for medical devices)**

Respondents were asked to rate investigator-driven criteria by dividing 100 points across 5 criteria potentially relevant in selecting trial sites for phase III studies:  
(Pharma, Biotech, CROs, CTUs, answer for phase III studies)  
(Medical device and all others answer for phase IV)  
Bars represent mean and 95% Confidence Interval (N=341)

There was evidence of a statistically significant difference in the level of importance among the 5 criteria ( $P < 0.0001$ )

**Table 4: Environment-driven criteria in selection of trial sites of phase II–III study sites (phase III–IV for medical devices)**

Respondents were asked to rate environment-driven criteria by dividing 100 points across 6 criteria potentially relevant in selecting trial sites for phase III studies:  
(Pharma, Biotech, CROs, CTUs, answer for phase III studies)  
(Medical device and all others answer for phase IV)  
Bars represent mean and 95% Confidence Interval (N=341)

There was evidence of a statistically significant difference in the level of importance among the 6 criteria ( $P < 0.0001$ )

**Table 5: Hospital-driven criteria in selection of phase II–III study sites (phase III–IV for medical devices)**

Respondents were asked to rate Hospital driven criteria by dividing 100 points across 6 criteria potentially relevant in selecting trial sites for phase III studies:  
(Pharma, Biotech, CROs, CTUs, answer for phase III studies)  
(Medical device and all others answer for phase IV)  
Bars represent mean and 95% Confidence Interval (N=342)

There was evidence of a statistically significant difference in the level of importance among the 6 criteria ( $P < 0.0001$ )

### Figure 1: Hypothesis about trial site selection criteria

Four categories of levers potentially impacting trial site selection were identified. Survey weighed relevance across these four levers, then drilled down for weight within each sub-category.

### Figure 2: Respondent's Organization

Respondents were asked to answer the question: "Please indicate which organisation most closely resembles yours"

Bars show percent distribution of 485 individual responses

#### Abbreviations

- Pharma = Industry: Pharmaceutical Company
  - CRO = Clinical Research Organisation
  - CTU = Academic Clinical Trial Unit
  - Biotech = Industry: Biotechnology Company
- Medical Devices included: Medical Devices, Radiological, Electro-medical or HealthCare Information Technology

"Other" included following self-reported categories:

- Respondent working for a mixed portfolio industry with either Pharma/Biotech portfolio or Pharm/Medical Device portfolio (self reported)
- Regulatory/Clinical Consultant
- Hospital or private clinic

### Figure 3

#### Left Panel: Respondent hierarchy

Respondents were asked to answer the question: "Please indicate the position which most closely resembles yours"

Chart shows percent distribution of 485 individual responses

VP = Vice President

"Others" were respondents who wanted to be more specific in their titles:

- Global Study Manager/Clinical Research Associate
- Regulatory Affairs/ Regulatory in a Clinical department/ Good Clinical Practice Quality Assurance Manager, or Director/ Safety Pharmacovigilance Officer
- Medical Affairs/ Medical Director/Clinical Director/Global Scientific Affairs
- General Manager
- "Professor or Lecturer"

#### Right Panel: Respondent organisation's decision-making process

Respondents were asked to answer the question: "Please indicate which most closely resembles how trial site selection decisions are made at your institution"

Chart shows percent distribution of 485 individual responses

Other included:

- My staff decides
- Decision outsourced to CRO
- CRA decides
- Decisions according to Standard Operation Procedures
- Many people involved in decision, or Study Team decides
- Our affiliates decide

### Figure 4

**Upper Panel**

**Accessibility and transparency of all types of information required to make trial site selection decisions - Twelve country rank (N=296)**

Respondents were asked to rate twelve countries for the accessibility and transparency of information (of all types) required to make trial site selection  
Bars represent mean and 95% Confidence Interval

Statistically significant difference in satisfaction across EU countries (P = 0.0001)

**Lower Panel**

**Predictability and speed of Ethics Committees and IRBs for phase II–III multi-centre RCTs - Twelve country rank (N=296)**

Respondents were asked to rate twelve countries for the speed of their ethics committees & IRBs for phase III (3) multi centric RCTs  
Bars represent mean and 95% Confidence Interval (number of respondents in parentheses)

Statistically significant difference in satisfaction across EU countries (P = 0.0001)  
IRB = institutional review board

**Figure 5: Trial Site Desirability by country**

Trial Site Desirability “Index” - Nine Country Rank

Respondents were asked to provide their "personal perception" ranking of the desirability of running trials in 9 countries, ranking them from (1) “most desirable” country to (9) “least desirable” country (if needed, they could click "no opinion" in up to three countries they know the least)

Data are presented as whisker-box plot of median and lower and upper quartile

There was evidence of a statistically significant difference in the perceived desirability of running trials across EU countries (P = 0.0001)

**Figure 6**

**Left Panel: Likelihood of selecting trial site given relevant information**

Respondents were asked to rate their level of agreement with the statement:  
“I am much more likely to select a trial site if I have all of the relevant Investigator and Site specific information easily available to me”  
Chart represents percent response (N=253)

**Right Panel: Usefulness of trial site web site information**

Respondents were asked to pick the statement that they felt closest to with reference to the assertion that “it would be useful to have relevant trial information readily visible in a dedicated public section the Hospital's web site (Facilities, equipment, personnel qualification, Ethics Committee and Institutional Review Board timings, contact people for trials, etc.)

European Trial Site Selection Criteria - The SAT-EU Study™  
October 6<sup>th</sup> 2013

## Factors Influencing Clinical Trial Site Selection in Europe: The Survey of Attitudes towards Trial sites in Europe (The SAT-EU Study™)

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**Authors' contributions**

MG: survey design and implementation; critical data analysis; manuscript drafting; overall project supervision

RT: survey design; statistical analysis; final manuscript editing

MM: survey design and implementation; survey advertising and data collection; critical data analysis; final manuscript editing

BC: survey design and implementation; survey advertising and data collection; critical data analysis; final manuscript editing

AP: survey design and implementation; survey advertising and data collection; critical data analysis; final manuscript editing

GG: survey design and implementation; critical data analysis; final manuscript editing

GA: survey design and implementation; critical data analysis; manuscript drafting; overall project supervision

**Data Sharing**

Extra data is available in the form of raw survey data, providing individual (blinded) responses for each of 485 respondents. This data can be accessed either directly on the Survey Monkey platform or downloaded to excel from Survey Monkey. Our statistical analysis is also available upon request. Extra data is available by emailing [giuseppe.ambrosio@ospedale.perugia.it](mailto:giuseppe.ambrosio@ospedale.perugia.it)

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## European Trial Site Selection Criteria - The SAT-EU Study™

### Abstract (300 words)

**Objectives:** Applications to run clinical trials in Europe fell 25% between 2007 and 2011. Costs, speed of approvals, and shortcomings of European Clinical Trial Directive are commonly invoked to explain this unsatisfactory performance. However, no hard evidence is available on the actual weight of these factors, nor has it been previously investigated whether other criteria may also impact clinical trial site selection.

**Design:** The SAT-EU Study™ was an anonymous, cross-sectional Web-based survey that systematically assessed factors impacting European clinical trial site selection. It explored 19 factors across investigator-, hospital-, and environment-driven criteria, and costs. It also surveyed perceptions of the European trial environment.

**Setting and Participants:** Clinical Research Organizations (CROs), academic Clinical Trial Units (CTUs), and Industry invited to respond.

**Interventions:** None

**Outcome measures:** Primary: Weight assigned to each factor hypothesized to impact trial site selection and trial incidence; Secondary: Desirability of European countries to run clinical trials

**Results:** Responses were obtained from 485 professionals in 34 countries: 49% from BioPharma, 40% from CTUs or CROs. Investigator-, environment-, and hospital-dependent factors were rated highly important, costs being less important ( $P<0.0001$ ). Within environment-driven criteria, pool of eligible patients, speed of approvals, and presence of disease-management networks were significantly more important than costs or government financial incentives ( $P<0.0001$ ). The pattern of response was consistent across respondent groupings (CTU vs. CRO vs. Industry). Considerable variability was demonstrated in the perceived receptivity of countries to undertake clinical trials, with Germany, United Kingdom, and the Netherlands rated the best trial markets ( $P<0.0001$ ).

**Conclusions:** Investigator-dependent factors and ease of approval dominate trial site selection, while costs appear less important. Fostering competitiveness of European clinical research may not require additional government spending/incentives. Rather, harmonization of approval processes, greater visibility of centres of excellence, and reduction of “hidden” indirect costs, may bring significantly more clinical trials to Europe.

**Article summary (292 words)**

**Article focus**

- Applications to perform clinical trials in the EU fell 25% from 2007 to 2011, with bureaucracy, the EU clinical trial directive 2001/20/EC, and costs reportedly to blame. Yet, the clinical research community lacks a systematic assessment of the relative weight of these and other criteria that may impact the viability of conducting clinical trials in Europe.
- The SAT-EU Study compiled the input of 485 decision makers to: (a) systematically evaluate 19 factors possibly impacting site selection for multicentre trials for which Europe is under consideration, and (b) to assess the relative desirability of doing trials in 12 European countries. The web-based survey was blinded and response choices were scrambled

**Key Messages**

- Costs, and even more so government incentives, carry a surprisingly low weight, while investigator- and environment-dependent factors dominate trial site selection decisions
- Not previously highlighted is the fact that the viability of conducting trials in Europe is also a function of the availability of critical information to get centres recruited and trials started, such as via participation in Disease Area Networks and web research portals
- Germany, UK, and the Netherlands are seen as the best trial markets

**Strengths and Limitations**

- *Strength:* We provide systematic evidence across a large sample of expert professionals indicating that fostering competitiveness of European clinical research may not require additional government spending/incentives. Carefully crafted harmonization of approvals, greater visibility of centres of excellence via disease networks/the web, and reduction of “hidden” costs are more likely to boost competitiveness of European clinical research
- *Limitations:* Consistent with voluntary surveys, we could only analyse responses provided by those interested in replying, and therefore cannot exclude that other points of view may have emerged from those who did not participate; our questionnaire may also have missed potentially important factors

## Introduction

Europe has consistently expressed a desire to maintain and improve clinical trial competitiveness,<sup>1-3</sup> most recently by advocating a “European Research Area” in which “researchers, scientific knowledge and technology circulate freely.”<sup>4</sup> A major component of the European governance for clinical research, European Clinical Trial Directive 2001/20/EC (CTD) was intended to support this goal, focussing on the harmonisation of research processes across EU member states.<sup>5-9</sup> However, the CTD failed to achieve its intended impact on the simplification and harmonization of administrative provisions governing clinical trials<sup>9</sup>, and thus on the level of European clinical research activity.<sup>2,10-11</sup> In fact, from 2007 to 2011, the number of clinical trial applications in Europe fell 25%<sup>12</sup>. Accordingly, although concerted calls for further CTD revisions continue<sup>13-14</sup> and recommendations awaiting member state review have been made by European Commission<sup>6</sup> and endorsed by scientific societies,<sup>15</sup> it is not clear which specific recommendations should be implemented or prioritized at either national or pan-European level.

Much of this uncertainty stems from insufficient understanding of the key drivers determining decision made by the healthcare industry, academic clinical trial units (CTUs), and clinical research organizations (CROs) in selecting European trial sites. Furthermore, although it is widely believed that costs and speed of approval are key factors influencing clinical trial incidence in Europe,<sup>6,16</sup> the relative weight of these and other important criteria is poorly understood. To our knowledge, no published studies have examined country and site selection criteria for trials conducted in Europe. Evidence is therefore needed to improve our understanding of stakeholders’ decision-making process.

The Survey of Attitudes towards Trial sites in Europe (The SAT-EU Study™) was established as a non-profit collaborative effort to systematically assess factors

impacting clinical trial site selection in Europe. We also investigated whether trial selection needs differ between academic and commercial sponsors. Finally, the survey sought to explore perceptions of the current European trial environment, and to identify areas for future improvement.

**Methods**

*Survey design*

The SAT-EU Study was an anonymous web-based cross-sectional survey undertaken between September 26<sup>th</sup> 2011, and January 21<sup>st</sup>, 2012. It included all stakeholder groups involved in clinical trial site selection, i.e., BioPharma companies, Medical Device manufacturers, CROs, and CTUs. The survey sought to capture information on both early- and late-phase studies. Late-phase studies were defined as phase III for CTUs, BioPharma and their sub-contractors (i.e., CROs), and phase IV for other participants (e.g. medical device companies).

A multi-stage approach was used to develop the survey. First, we identified the main criteria expected to impact site selection. Second, we organized these in four broad categories: (i) investigator-related, (ii) hospital/Institution-related, (iii) country/environment-related, and (iv) costs (evaluated both separately and within the environment category). Third, the defined criteria underwent review and discussion with a small number of knowledgeable professionals to ensure that potentially relevant criteria had not been missed (Figure 1).

The study group then built an internet-based survey hosted on a freely-accessible online questionnaire software (Survey Monkey, Palo Alto, CA, USA). Before launching the survey, healthcare market research experts (The Planning Shop International, London, UK) reviewed the survey design to optimize content and minimize bias. Additionally, a pilot survey undertaken by 15 respondents in June 2011

was used to validate and refine question content and organisation.

### *Survey Procedure*

The survey consisted of 23 questions, which took some 20 minutes to complete. In sequence, questions asked participants to (1) provide demographic information anonymously (2) rate the importance of each of the hypothesized trial site selection criteria for Europe as a whole, (3) provide perception of the trial environment in 12 European countries, and (4) rank areas of potential improvement. Participants' feedback was assessed using a multiple-choice format, requiring respondents to provide a single response of rank. The full set of questions is accessible at [http://www.sbg-marcom.ch/sat-eu/Study\\_plan.html](http://www.sbg-marcom.ch/sat-eu/Study_plan.html). The order of presentation of individual responses to each question was scrambled across respondents to minimise response bias. At the end of each section, a response box allowed participants to provide open text comments, available as an "online supplement". Results of the survey were thoroughly reviewed among the study group, and subsequently discussed with a 25-member expert panel in Brussels on November 2012.

The survey was advertised through Industry and Clinical Trial Associations, online communities, social networks, and personal contacts of the SAT-EU Study group<sup>17</sup>, so that the precise number of people invited to participate is not known. No remuneration was provided to participants, but respondents were offered a summary of survey results once available.

### *Statistical Analysis*

Given the descriptive nature of the SAT-EU study design, we did not formally estimate a required sample size. Instead, we sought to obtain at least 150 completed questionnaires from across the four stakeholder groups. Results are primarily

presented descriptively as means (and 95% confidence intervals (95% CI)), or medians (and upper and lower quartiles), as appropriate to show results by group or country. Where data were available, responses were compared across three survey respondent groupings (i.e. CTU vs. CRO vs. industry), and across responses within each survey question, using one-way analysis of variance.

**Results**

A total of 485 individual responses were obtained, with participants providing responses to 72% of questions on average. Responders represented over 100 different institutions, including over 50 pharmaceutical, biotechnology or medical device firms, and over 20 CROs and CTUs.

*Respondent Demographics*

Respondents represented over 37 countries, the top five contributors being Italy, USA, UK, Germany, and Spain (Table 1). Participants were almost evenly split between BioPharma (49%) and CROs/CTUs (40%) (Figure 2). In terms of hierarchy/job description, 43% were vice-president, director, or manager in a research or marketing position, and an additional 20% were head of a CTU (Figure 3, Left Panel). The majority of respondents described themselves as being directly involved in trial site selection decisions; almost two-thirds either personally headed, or sat on the trial site selection committee of their organization (Figure 3, Right Panel). Importantly, most respondents were the final decision makers, stating that they were either the “overall final decision maker”, or that trial site selection decisions were “entirely at (their) discretion”.

*Relevance of investigator, environment, hospital, and costs criteria*

Respondents were asked to divide 100 points (reflecting their perceived level of

importance) across four categories of factors impacting trial site selection. For both early- and late-phase trials (as defined in Methods), factors pertaining to the investigator, the hospital/unit, and the environment, were rated at a high level of importance (25 or above) (Table 2). When combined, investigator- and hospital-dependent levers were reported to be instrumental in trial site choice for both early- and late-phase studies (average weight 60/100 and 57/100 respectively). In contrast, cost factors were considered to be less important for both early- and late-trials ( $P<0.0001$ ) (Table 2). This pattern of response was consistent across survey respondent groupings (i.e. CTU vs. CRO vs. industry; not shown).

#### *Investigator-Driven Criteria*

Respondents were asked to assign 100 points across five investigator-related criteria. There was a statistically significant difference in the level of importance of the factors tested, with investigator track record in prior trials, experience in similar studies, and interest in study scoring a level of importance of 20 or above, while concurrent trial workload, and publication track record were significantly less important ( $P<0.0001$ ) (Table 3). The pattern of response was again consistent across survey respondent groupings (not shown).

#### *Environment-Driven Criteria*

To explore environmental dynamics, respondents were asked to assign 100 points across six environment-related criteria. Market size/pool of eligible patients in the region, speed of approvals, and presence of disease management networks, were assigned a greater level of importance. In contrast, costs of running trials, and particularly government financial/tax incentives were considered to be of significantly lower importance ( $P<0.0001$ ) (Table 4). Also in this case, the pattern of response was consistent across survey respondent groupings (not shown).

#### *Hospital-Driven Criteria*

In this domain, 100 points had to be assigned across six criteria that explored

characteristics of the specific hospital/unit where a clinical trial may potentially be run. There was a statistically significant difference in the level of importance of hospital-driven criteria, whereby site personnel experience and training, respondent's previous experience with site, and availability of facilities and equipment required by trial scored above 20 ( $P<0.0001$ ). In contrast, site personnel language capabilities and hospital quality assurance process were significantly less important (Table 5).

*Perception of European Trial Environment*

Our survey showed a statistically significant difference in respondents' perceived desirability of running clinical trials across the twelve EU countries tested, i.e., Europe's top 5 healthcare markets (Germany, France, Italy, the UK, and Spain), large east European markets (Poland, Hungary, Czech Republic), plus Netherlands, Belgium, Switzerland, and Austria. For both accessibility and transparency of all information required to run clinical trials (Figure 4, Upper Panel), and availability of equipment (not shown), Germany, UK and the Netherlands were the top three scorers. With regard to predictability and speed of Ethics Committees, Belgium was the top scorer, followed by Germany and the Netherlands (Figure 4, Lower Panel). In terms of overall trial site "desirability", respondents scored Germany as the most desirable trial location, followed by the Netherlands and UK ( $P=0.0001$ ) (Figure 5).

*Possible Improvements*

Two questions tested the hypothesis that making a site more visible would be desirable from the decision-makers' perspective. We found that 83% of respondents would have been "much more likely" to include a site if all relevant investigator- and hospital-related information were readily available (Figure 6, Left Panel). Furthermore, 75% believed that web-site information would be either "definitely welcome", or "useful most of the time" (Figure 6, Right Panel).

European Trial Site Selection Criteria - The SAT-EU Study™  
October 6<sup>th</sup> 2013

For peer review only

**Discussion**

The SAT-EU Study<sup>TM</sup> was a web-based survey designed to identify perceived drivers and hurdles associated with conducting clinical trials in Europe. We obtained responses from over four hundred participants in key stakeholder groups, i.e. BioPharma industry, medical device manufacturers, CROs, and CTUs. The vast majority of countries actively involved in clinical trials were represented, while most respondents were key decision makers in their organizations. These features allowed us to get direct and potentially relevant insights into the reasoning behind site selection for clinical trials.

Recent years have seen much public policy discussion on the need to foster Europe’s role in medical research, and to rekindle its dwindling attractiveness for investment in clinical trials.<sup>18-20</sup> Various strategies have been proposed based on a “common sense” approach. Whilst possibly sound, policy recommendations were typically not founded on a systematic understanding of factors impacting clinical trial site selection. Indeed, one could argue that, borrowing from the rigour of its own discipline, medical policy decisions at all levels ought to be “evidence-based”. Regretfully however, this approach seems to be largely absent. To our knowledge, the SAT-EU study is the first effort aimed at systematically investigating factors impacting trial site attractiveness across Europe. Given the survey’s size, the variety of domains explored, the number of countries and organizations involved, and the prevalence of senior decision makers, our results may provide insight into “real world” trial site decisions.

Our study has several key findings. First, there was evidence of considerable variability in the perceived receptivity of European countries to undertake clinical trials, Germany, United Kingdom, and the Netherlands being rated the best markets. Reasons for greater appeal of certain countries are multiple. Larger countries could be

more attractive because of greater patient recruitment potential, and in prospect, because of the size of their markets. However, country size does not entirely explain the phenomenon, given the excellent results of small countries such as the Netherlands, and the low score of large countries such as Italy or Spain. Our survey sheds some light on this by pointing to the negative impact of administrative burden on clinical trial competitiveness. This is not only a concern at country level. Central to this discussion is the notion that the time required to collect information to determine a site's feasibility for inclusion in a trial, and to get it started, is also critical. Hence, the high weight placed on a site's proven track record in efficiently delivering results, which bears a relationship to specialized clinical research centres, and equally important, to the ability of clinical trial sponsors and organizers to access all of the required information quickly and effectively. Accordingly, the downsides of operating within a sub-optimal regulatory environment may not prejudice selection of an otherwise visible and competent investigator, whose trial site information is readily available and who is able to recruit the required patients. A third important finding of our survey is that contrary to a widely held tenet, costs of running trials - often invoked to explain why industry is going outside Europe<sup>6,16</sup> - as well as government incentives/tax breaks, are not the main considerations when selecting European sites. In other words, it would seem from stakeholders' feedback and follow-up discussions that to the extent that European centers may be excluded from a trial, the likely culprit is the hidden costs associated with excessive administrative time required to get a trial site up and running, not the high fees per enrolled patient. Although apparently surprising, the limited impact of costs needs to be considered against the backdrop of the various issues to which our survey tried to provide a response. Indeed, in addition to "direct" costs, a major negative factor is represented by indirect, or "hidden" costs, such as those characterized by time lost through layers of bureaucracy, slow recruitment by sites, or poor overall site performance. Hence, the importance of not only bureaucracy, but also of the level of training and trial expertise at sites. Additionally, the notion that

investments in clinical trials in Europe cannot be easily improved through government incentives or tax breaks may have important implications in terms of public policy. Comments obtained through our survey seem to indicate that stakeholders would like a single European “trial market” allowing them to gear trial site selection to expert investigators and to optimal patient recruitment, unobstructed by heterogeneous regulations or hurdles to obtaining crucial information. Participants expressed this need in two main ways. First, from a regulatory or “macro” perspective, they expressed desire for easier approval processes with less national variability and stronger pan-European element. This may indicate ethical committee approval timeframes, as well as institutional approvals at site level. Second, from a clinical research or “micro” perspective, respondents want access to transnational networks of disease-area experts, through visibility of experienced trial units via the internet and/or via participation in disease networks.

More than 50 years ago, the founders of the European Union envisioned a single market at the core of the European project. Despite this, a “single market” vision for clinical research did not develop as envisaged. This is damaging to an industry in which much of the investment in clinical trials is by necessity multinational. Indeed, Europe’s 2020 growth strategy calls for 3% of its Gross National Product to be invested in research and development (R&D) by 2020<sup>21</sup>. If this goal is to be achieved, BioPharma - the European sector with the highest R&D/Sales ratio<sup>22</sup> - should be allowed to invest in Europe without facing unnecessary roadblocks. Given the size of its healthcare market, its aging population, its well-established pharmaceutical industry, and the quality of its research centres and investigators, Europe has a formidable comparative advantage in clinical research. Individual European member states are well poised to take advantage of this by making the EU more competitive in clinical research. They should be encouraged to do so, not simply by investing in incentives or tax breaks, but by implementing revisions to the CTD that are under consideration by member states, and by legislating removal of unhelpful bureaucratic barriers at national

level. Improving hospital contracting, such as via national or even pan-European contract templates, would also significantly reduce administrative burden, speed up trial start, and make the European landscape significantly more competitive. On their part, the research community and relevant national bodies have a parallel imperative to ensure that hospitals and institutions are organised and networked more effectively, and that there is adequate training of trial staff. They need to ensure that clinical centres wishing to undertake more research are made more visible to industry and to international research communities, through dedicated research portals on their web sites, or by creating and/or joining disease networks. Finally, given that selected countries are consistently scored above others, a best practice audit of administrative provisions governing and supporting clinical trials in countries such as Germany, the UK, the Netherlands<sup>14</sup> would be helpful for drawing policy implications for other countries. The case for action rests on the realization that evidence-based policy is indeed possible in this arena. Learning from what is working successfully will facilitate the road to creating a more welcoming environment for clinical research in Europe.

## Limitations

Consistent with voluntary surveys, we could only analyse responses provided by those who were interested in replying, and therefore we cannot exclude that other points of view may have emerged from those who did not participate. Nonetheless, it is rather reassuring that the responses were gathered through a fairly large number of professionals who belonged to a variety of organizations from a number of countries, and who were for the most part the final decision makers in the process. However, given that participation was largely through professional bodies and web-based communities, we are unable to provide an estimate of our coverage. Whilst we took care in designing a survey that focused on the key determinants of trial site selection, we may have missed potentially important issues. We tried to minimize this through preliminary survey review and refinement with the help of external experts. [Also,](#)

although we aimed at obtaining data relative to both industry-sponsored and not-for-profit clinical trials, it is possible that responses preferentially captured the former. In addition,<sup>7</sup> some of our questions ~~in relation~~relating to process and speed of approval may need further research to determine the root issues, as problems differ from country to country, and have to be weighed against the need to ensure that patient safety remains unprejudiced.

**Conclusions**

Our study indicates that fostering European clinical research and attracting more trials to Europe does not require additional government spending. Instead, we believe our findings support a more harmonised national adoption of the clinical trial approvals process, greater visibility of transnational networks of disease experts, and greater accessibility to research system at national and pan-European levels. Potential models for improvement include harmonization of ethical and institutional approvals systems, including aligned hospital contracting and greater visibility of centres of excellence, which may bring significantly more clinical research to Europe. Europe needs growth, and clinical research can play its part in directly stimulating economic activity while simultaneously boosting European innovation.

## Acknowledgments

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Applied Clinical Trials (ACT)

<http://www.appliedclinicaltrials.com/>

European Forum for Good Clinical Practice (EFGCP)

<http://www.efgcp.be>

European Federation of Pharmaceutical Industry Associations (EFPIA)

<http://www.efpia.eu/>

European Biotech Industry Association (EuropaBio)

<http://www.europabio.org/>

Perugia University, Italy

<http://facolta.unipg.it/medicina/>

Drug Information Association (DIA)

<http://www.diahome.org/DIAHome/Home.aspx>

Virtuoso Consulting, Geneva, Switzerland

<http://www.virtuoso.ch/model.html>

European Vision Institute Clinical Research Network (Disease Network)

<http://www.evicr.net>

EUCOMED Clinical Trial Interest Group

<http://www.eucomed.be/>

Pharma IQ

<http://www.pharma-iq.com/>

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**Competing Interests**

All co-authors work in the area of healthcare, either academia or consulting, and as such have all been, or are involved in, the initiation, execution or interpretation of clinical trials. Accordingly, all co-authors have an intellectual/academic interest in seeing the European Clinical trial industry enhance its competitiveness. None of the authors however, stands to gain any more than any other member of the European healthcare community from the implementation of any of the recommendations made in the manuscript. We declare no other conflict of interest, and no other relationships or activities that could appear to have influenced the submitted work.

The study group has received acknowledgement permission from each of the institutions acknowledged for having helped to collect survey participants. Participation in the survey was voluntary and not associated with any remuneration.

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Table and Figure Legend

Table 1: Respondent work location

Table 2: Levers impacting trial site selection for early and late trials

Respondents were asked to divide 100 points across the below 4 levers impacting their trial site selection for early phase studies:

(Pharma, Biotech, CROs, CTUs, answer for phase II studies)  
(Medical device and all others answer for phase III studies)

and then for later phase studies:

(Pharma, Biotech, CROs, CTUs, answer for phase III studies)  
(Medical device and all others answer for phase IV studies)  
Bars represent mean and 95% Confidence Interval (N=341)

There was evidence of a statistically significant difference in the level of importance among the 4 factors ( $P < 0.0001$ )

Table 3: Investigator-driven criteria in selection of trial sites of phase II–III study sites (phase III–IV for medical devices)

Respondents were asked to rate investigator-driven criteria by dividing 100 points across 5 criteria potentially relevant in selecting trial sites for phase III studies:

(Pharma, Biotech, CROs, CTUs, answer for phase III studies)  
(Medical device and all others answer for phase IV)  
Bars represent mean and 95% Confidence Interval (N=341)

There was evidence of a statistically significant difference in the level of importance among the 5 criteria ( $P < 0.0001$ )

Table 4: Environment-driven criteria in selection of trial sites of phase II–III study sites (phase III–IV for medical devices)

Respondents were asked to rate environment-driven criteria by dividing 100 points across 6 criteria potentially relevant in selecting trial sites for phase III studies:

(Pharma, Biotech, CROs, CTUs, answer for phase III studies)  
(Medical device and all others answer for phase IV)  
Bars represent mean and 95% Confidence Interval (N=341)

There was evidence of a statistically significant difference in the level of importance among the 6 criteria ( $P < 0.0001$ )

Table 5: Hospital-driven criteria in selection of phase II–III study sites (phase III–IV for medical devices)

Respondents were asked to rate Hospital driven criteria by dividing 100 points across 6 criteria potentially relevant in selecting trial sites for phase III studies:

(Pharma, Biotech, CROs, CTUs, answer for phase III studies)  
(Medical device and all others answer for phase IV)  
Bars represent mean and 95% Confidence Interval (N=342)

There was evidence of a statistically significant difference in the level of importance among the 6 criteria ( $P < 0.0001$ )

Figure 1: Hypothesis about trial site selection criteria

Four categories of levers potentially impacting trial site selection were identified.

Survey weighed relevance across these four levers, then drilled down for weight within each sub-category.

### Figure 2: Respondent's Organization

Respondents were asked to answer the question: "Please indicate which organisation most closely resembles yours"

Bars show percent distribution of 485 individual responses

#### Abbreviations

- Pharma = Industry: Pharmaceutical Company
  - CRO = Clinical Research Organisation
  - CTU = Academic Clinical Trial Unit
  - Biotech = Industry: Biotechnology Company
- Medical Devices included: Medical Devices, Radiological, Electro-medical or HealthCare Information Technology

"Other" included following self-reported categories:

- Respondent working for a mixed portfolio industry with either Pharma/Biotech portfolio or Pharm/Medical Device portfolio (self reported)
- Regulatory/Clinical Consultant
- Hospital or private clinic

### Figure 3

#### Left Panel: Respondent hierarchy

Respondents were asked to answer the question: "Please indicate the position which most closely resembles yours"

Chart shows percent distribution of 485 individual responses

VP = Vice President

"Others" were respondents who wanted to be more specific in their titles:

- Global Study Manager/Clinical Research Associate
- Regulatory Affairs/ Regulatory in a Clinical department/ Good Clinical Practice Quality Assurance Manager, or Director/ Safety Pharmacovigilance Officer
- Medical Affairs/ Medical Director/Clinical Director/Global Scientific Affairs
- General Manager
- "Professor or Lecturer"

#### Right Panel: Respondent organisation's decision-making process

Respondents were asked to answer the question: "Please indicate which most closely resembles how trial site selection decisions are made at your institution"

Chart shows percent distribution of 485 individual responses

Other included:

- My staff decides
- Decision outsourced to CRO
- CRA decides
- Decisions according to Standard Operation Procedures
- Many people involved in decision, or Study Team decides
- Our affiliates decide

### Figure 4

#### Upper Panel

**Accessibility and transparency of all types of information required to make trial site selection decisions - Twelve country rank (N=296)**  
Respondents were asked to rate twelve countries for the accessibility and transparency of information (of all types) required to make trial site selection  
Bars represent mean and 95% Confidence Interval

Statistically significant difference in satisfaction across EU countries (P = 0.0001)

**Lower Panel**  
**Predictability and speed of Ethics Committees and IRBs for phase II–III multi-centre RCTs - Twelve country rank (N=296)**  
Respondents were asked to rate twelve countries for the speed of their ethics committees & IRBs for phase III (3) multi centric RCTs  
Bars represent mean and 95% Confidence Interval (number of respondents in parentheses)

Statistically significant difference in satisfaction across EU countries (P = 0.0001)  
IRB = institutional review board

**Figure 5: Trial Site Desirability by country**  
Trial Site Desirability “Index” - Nine Country Rank

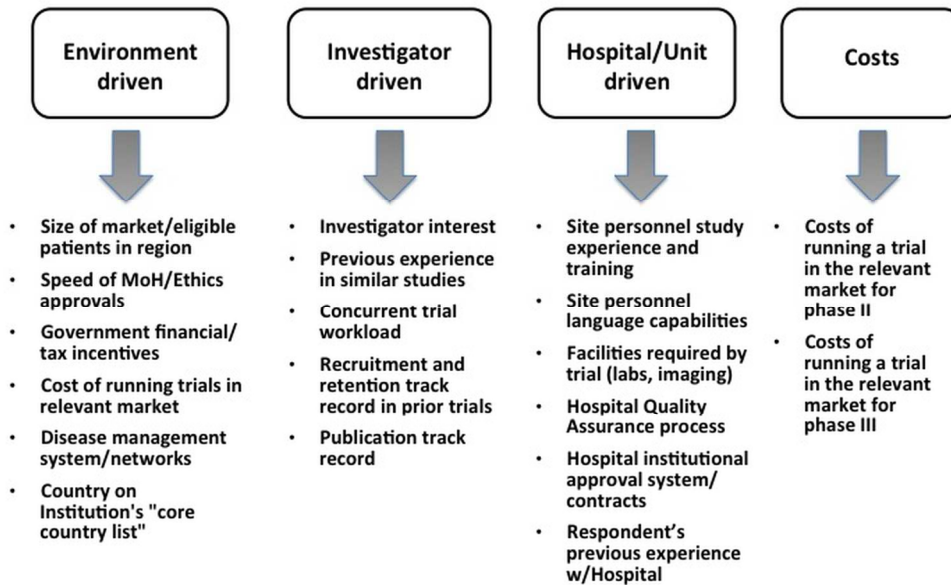
Respondents were asked to provide their "personal perception" ranking of the desirability of running trials in 9 countries, ranking them from (1) “most desirable” country to (9) “least desirable” country (if needed, they could click “no opinion” in up to three countries they know the least)  
Data are presented as whisker-box plot of median and lower and upper quartile

There was evidence of a statistically significant difference in the perceived desirability of running trials across EU countries (P = 0.0001)

**Figure 6**  
**Left Panel: Likelihood of selecting trial site given relevant information**  
Respondents were asked to rate their level of agreement with the statement:  
“I am much more likely to select a trial site if I have all of the relevant Investigator and Site specific information easily available to me”  
Chart represents percent response (N=253)

**Right Panel: Usefulness of trial site web site information**  
Respondents were asked to pick the statement that they felt closest to with reference to the assertion that “it would be useful to have relevant trial information readily visible in a dedicated public section the Hospital's web site (Facilities, equipment, personnel qualification, Ethics Committee and Institutional Review Board timings, contact people for trials, etc.)

*Figure 1*  
**Hypothesis about trial site selection criteria**

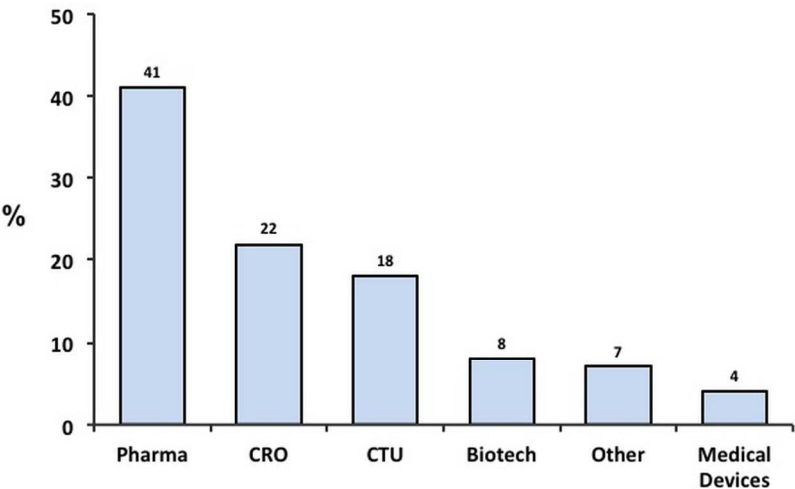


Hypothesis about trial site selection criteria

Four categories of levers potentially impacting trial site selection were identified.

Survey weighed relevance across these four levers, then drilled down for weight within each sub-category  
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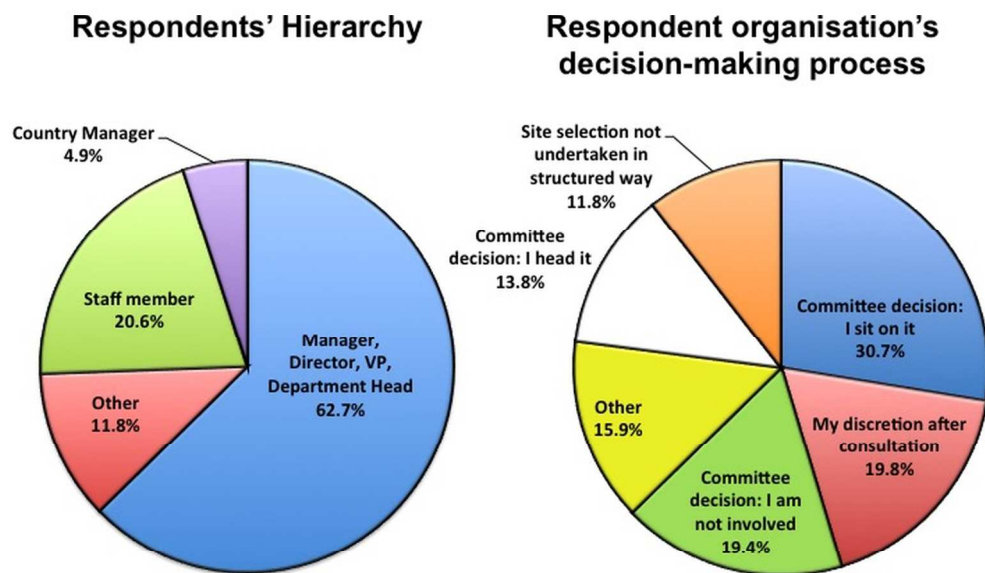
Figure 2  
Respondents' Organisation



Respondent's Organization

Respondents were asked to answer the question: "Please indicate which organisation most closely resembles yours"  
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Figure 3



Left Panel: Respondent hierarchy

Respondents were asked to answer the question: "Please indicate the position which most closely resembles yours"

Chart shows percent distribution of 485 individual responses

VP = Vice President

"Others" were respondents who wanted to be more specific in their titles:

- Global Study Manager/Clinical Research Associate
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- Medical Affairs/ Medical Director/Clinical Director/Global Scientific Affairs
- General Manager
- "Professor or Lecturer"

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Respondents were asked to answer the question: "Please indicate which most closely resembles how trial site selection decisions are made at your institution"

Chart shows percent distribution of 485 individual responses

Other included:

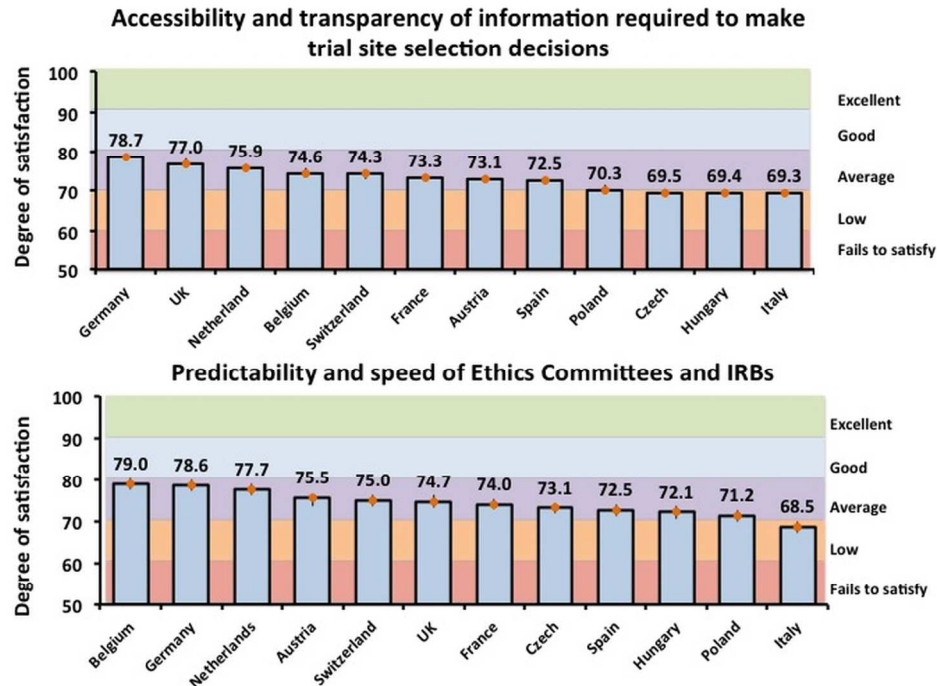
- My staff decides
- Decision outsourced to CRO
- CRA decides
- Decisions according to Standard Operation Procedures
- Many people involved in decision, or Study Team decides
- Our affiliates decide

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For peer review only

Figure 4



## Upper Panel

Accessibility and transparency of all types of information required to make trial site selection decisions - Twelve country rank (N=296)

Respondents were asked to rate twelve countries for the accessibility and transparency of information (of all types) required to make trial site selection

Bars represent mean and 95% Confidence Interval

Statistically significant difference in satisfaction across EU countries ( $P = 0.0001$ )

## Lower Panel

Predictability and speed of Ethics Committees and IRBs for phase II-III multi-centre RCTs - Twelve country rank (N=296)

Respondents were asked to rate twelve countries for the speed of their ethics committees & IRBs for phase III (3) multi centric RCTs

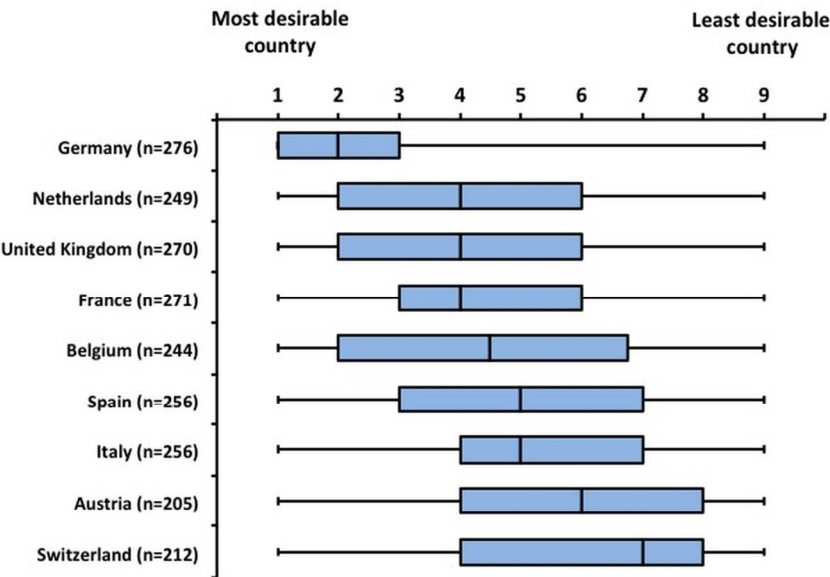
Bars represent mean and 95% Confidence Interval (number of respondents in parentheses)

Statistically significant difference in satisfaction across EU countries ( $P = 0.0001$ )

IRB = institutional review board

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Figure 5  
Trial Site Desirability by Country



Trial Site Desirability by country

Trial Site Desirability "Index" - Nine Country Rank

Respondents were asked to provide their "personal perception" ranking of the desirability of running trials in 9 countries, ranking them from (1) "most desirable" country to (9) "least desirable" country (if needed, they could click "no opinion" in up to three countries they know the least)  
Data are presented as whisker-box plot of median and lower and upper quartile

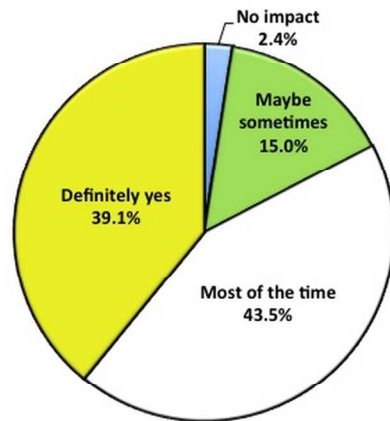
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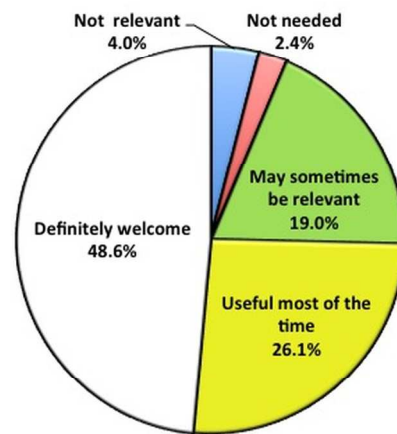


Figure 6

### Likelihood of selecting trial site given relevant information



### Usefulness of trial site web site information



Left Panel: Likelihood of selecting trial site given relevant information

Respondents were asked to rate their level of agreement with the statement:

"I am much more likely to select a trial site if I have all of the relevant Investigator and Site specific information easily available to me"

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Right Panel: Usefulness of trial site web site information

Respondents were asked to pick the statement that they felt closest to with reference to the assertion that

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